

Anakinra for the Treatment of Rheumatoid Arthritis

August 16, 2001

Agenda

- Overview
 - Roger M. Perlmutter, MD, PhD
- Clinical Experience
 - Moraye Bear, MS, MA
 - Pirow Bekker, MD, PhD
- Therapeutic Role of Anakinra
 - Stanley Cohen, MD

Proposed Indication for Anakinra

Anakinra is indicated for the reduction in signs and symptoms of active rheumatoid arthritis, in patients 18-years of age or older who have failed 1 or more disease-modifying antirheumatic drugs (DMARDs).

Anakinra can be used alone or in combination with other DMARDs.

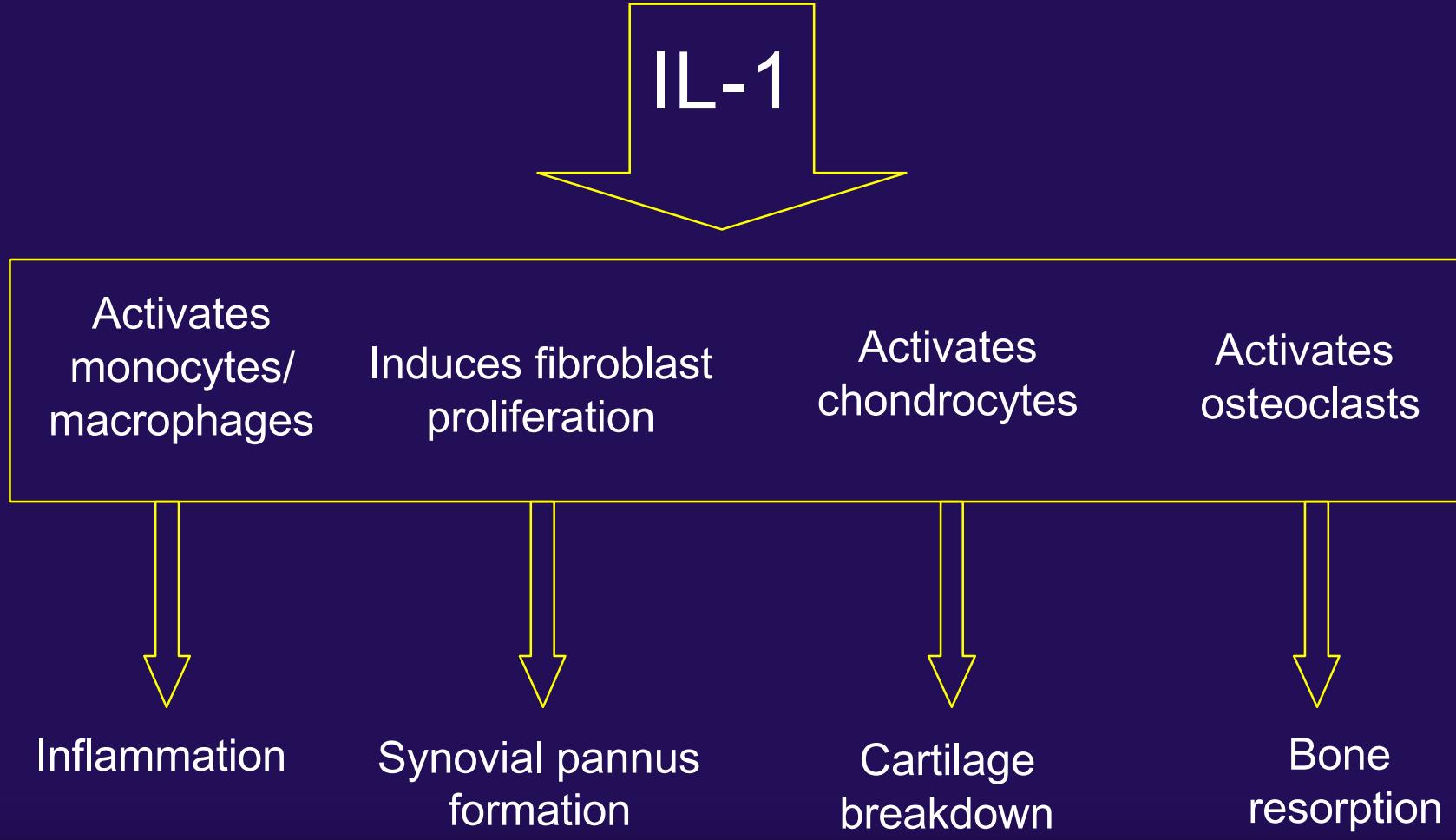
Cytokines and Cytokine Inhibitors in Rheumatoid Arthritis (partial list)

| Pro-Inflammatory | Anti-Inflammatory |
|------------------|-------------------|
| IL-1 | IL-1Ra |
| TNF-a | p55-sTNF-RI |
| IL-6 | p75-sTNF-RII |
| GM-CSF | IL-10 |
| IL-8 | TGFβ |

References

- Feldmann et al. (1993) Progress in Growth Factor Research 4, 247-255
- Feldmann et al. (1996) Annu. Rev. Immunol. 14, 397-440

IL-1: A Proinflammatory Cytokine



Arthritogenic Actions of Recombinant IL-1 and TNF α in the Rabbit: Evidence for Synergistic Interactions Between Cytokines In Vivo

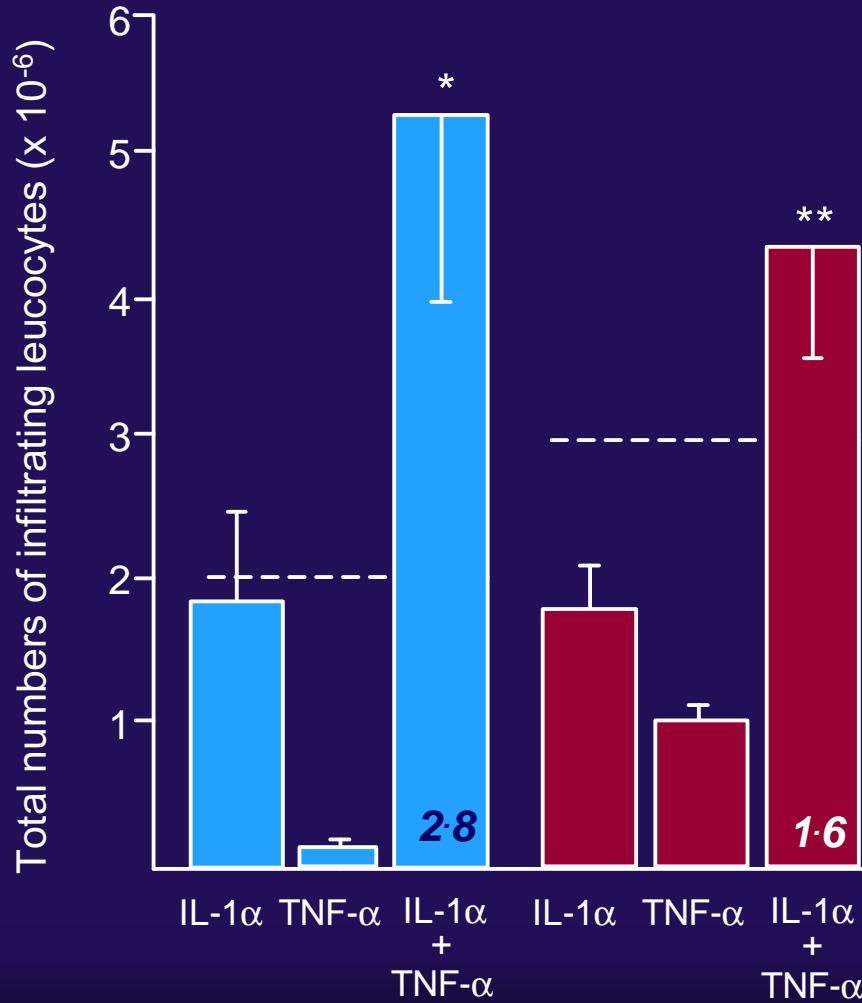


Fig. 4. Synergistic interaction between IL-1 and TNF.

The total numbers of PMNs (blue) or monocytes (red) in the joint cavity 24 h after injecting 10 ng IL-1 α , 250 ng TNF- α or a combination of cytokines is shown.

The results are expressed as mean \pm s.e.m. of 9 animals.

The figures in the lower part of the right hand columns give the degree of synergy compared with the sum of cellular accumulation produced by individual cytokines.

*P<0.02 compared to the number of PMN induced by IL-1 α . **P<0.001 compared to the number of monocytes induced by IL-1 α .

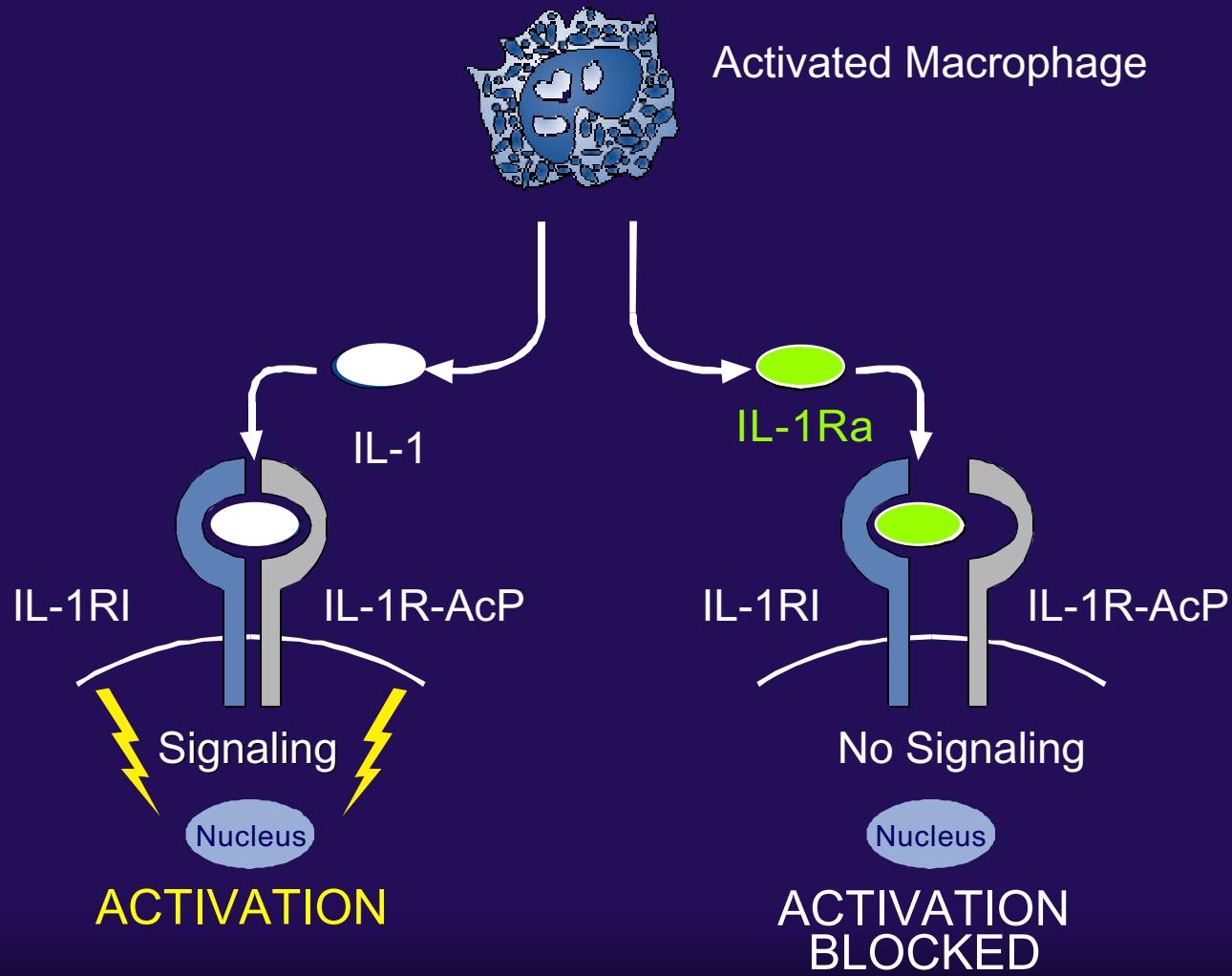
IL-1 Induces Chronic Arthritis

- Repeated intra-articular injections of IL-1 in rat knees induces arthritis
 - Chandrasekhar et al. Clin. Immunol. Immunopathol. 1990, 55:382-400
- Continuous infusion of IL-1 into rabbit knees induces arthritis
 - Feige et al. Int. J. Tiss. React. 1989, 11:225-38
- IL-1 injection or infusion triggers onset of arthritis in mice
 - Hom et al. J. Immunol. 1988, 141:834-841
 - Hom et al. Clin. Immunol. Immunopathol. 1990, 55:109-119
- Intraarticular expression of IL-1 β in rabbit synovium by gene transfer induces arthritis
 - Ghivizzani et al., J. Immunol. 1997; 159:3604-3612
- IL-1 α transgenic mice develop arthritis early
 - Niki et al., J. Clin. Invest. 2001, 107:1127-1135
- Mice lacking IL-1ra develop spontaneous arthritis
 - Horai et al., J. Exp. Med. 2000; 191:313-320

Endogenous IL-1Ra: A Naturally Occurring Antagonist of IL-1

- IL-1Ra
 - Is a member of IL-1 family
 - Is structurally related to IL-1
 - Is produced constitutively and during inflammation
 - Binds to IL-1 receptors (IL-1R)
 - Occupies but does not activate IL-1R
 - Does not allow docking of IL-1R Accessory Protein (AcP)
 - Is a pure receptor antagonist

IL-1Ra Blocks Cellular Activation



Animal Models of Arthritis: General Overview

Inject Type II
collagen, or
Adjuvant

Anakinra
Treatment
(SC, IP or infusion)

Assessments: paw
swelling, histology,
bone markers, x-ray



Arthritis
develops



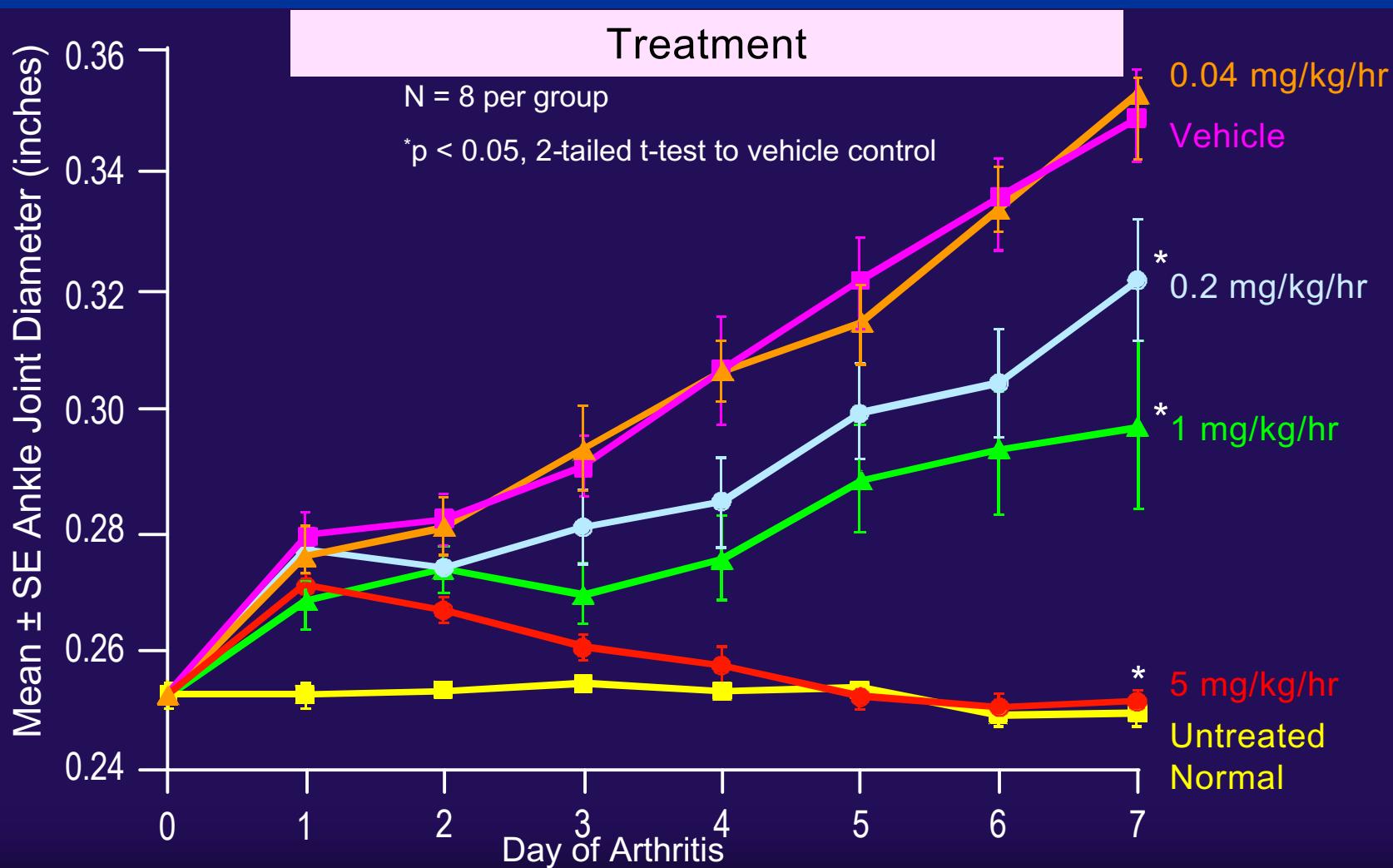
Therapeutic
Treatment
Period



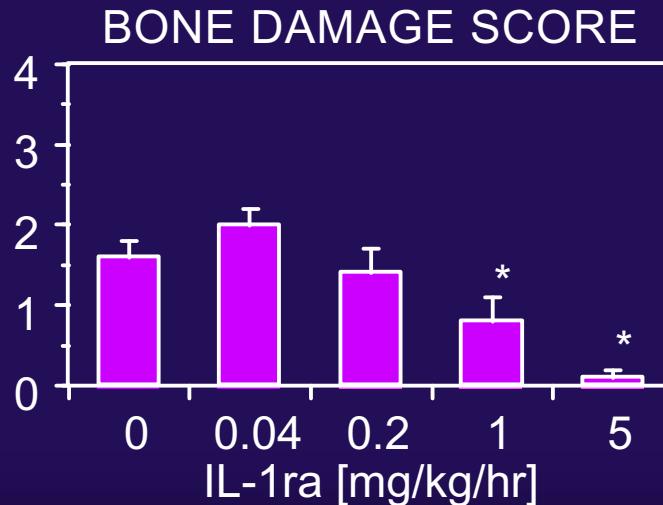
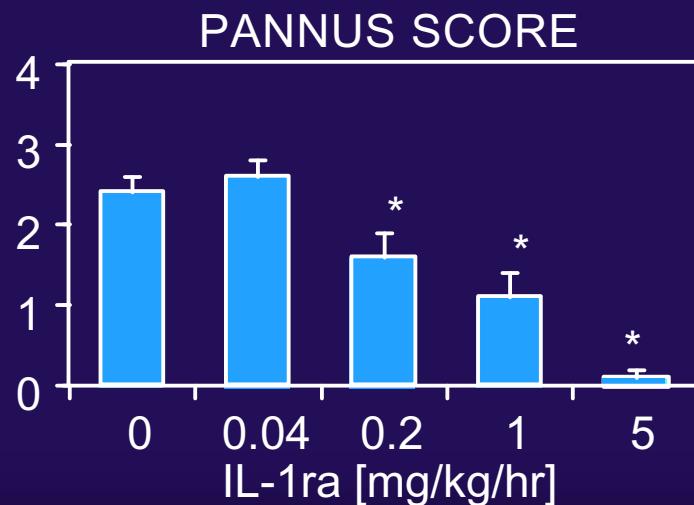
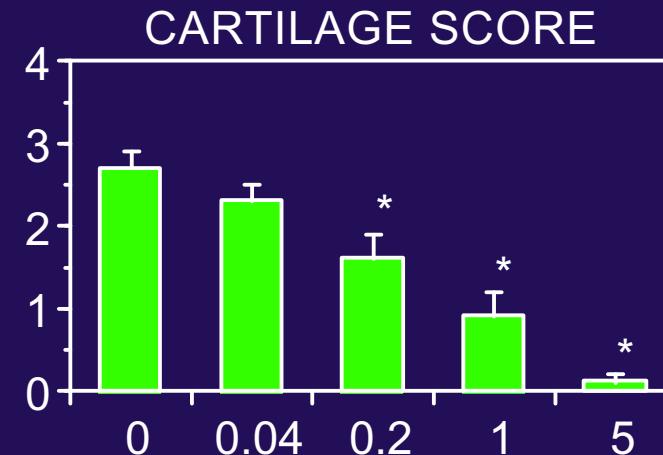
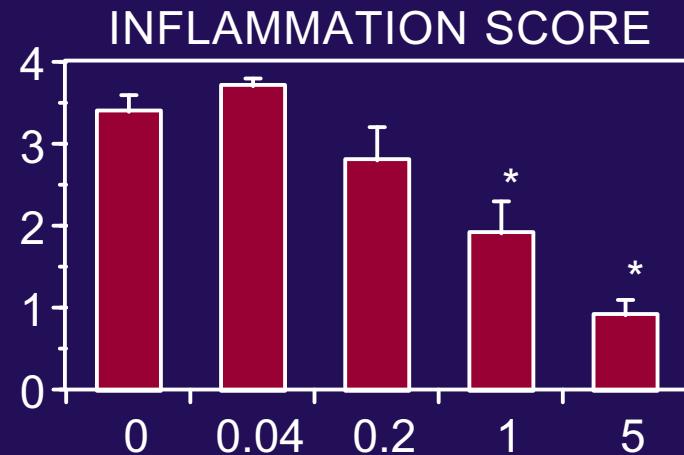
8 to 10 days

7 to 14 days

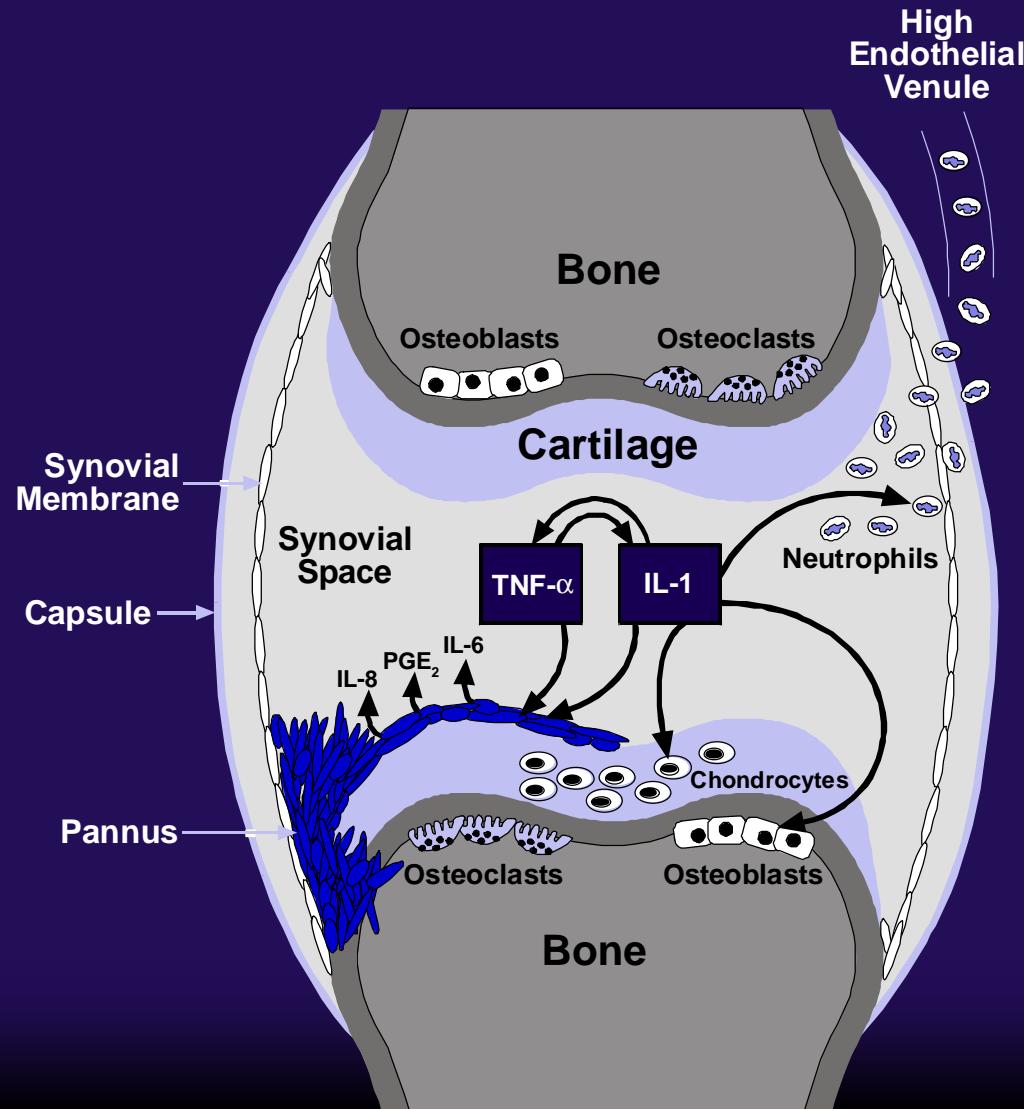
Collagen-Induced Arthritis: Treatment Effects on Inflammation



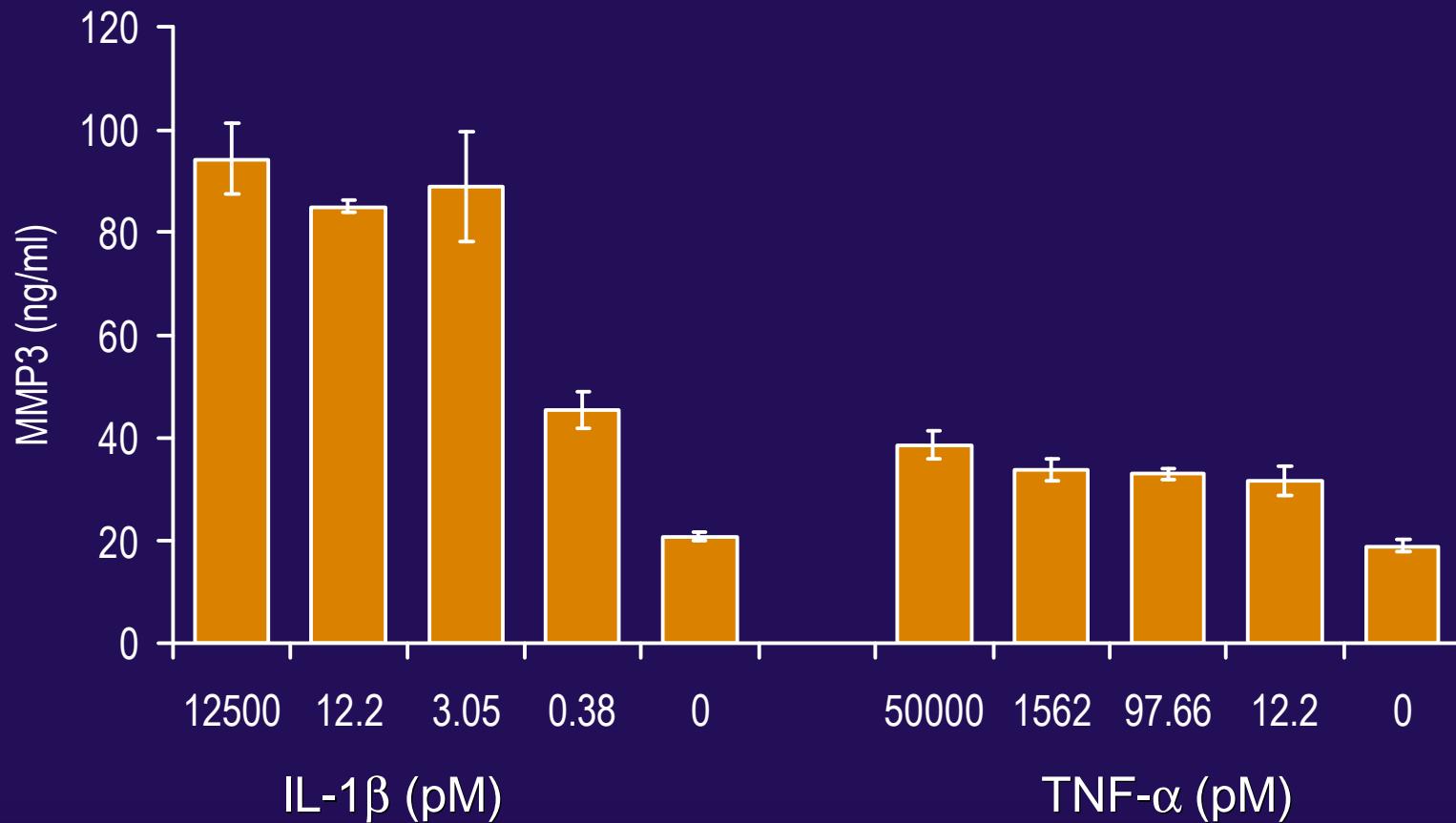
Collagen-Induced Arthritis: Treatment Effects on Histological Scores



IL-1 and TNF α : Proinflammatory Cytokines in the Rheumatoid Joint



Differential Regulation of MMP-3 Production by IL-1 β and TNF- α in Human Chondrocytes

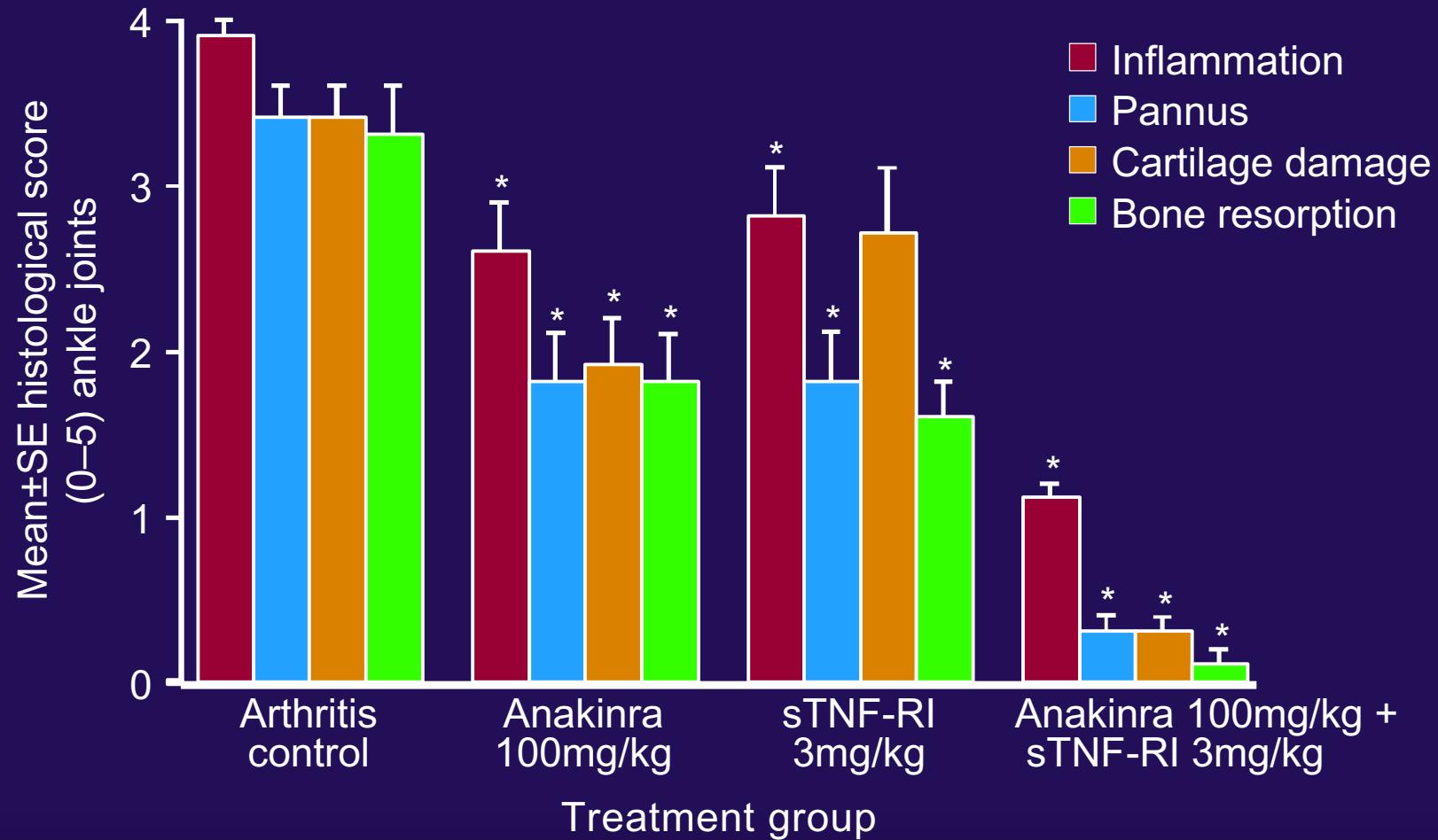


IL-1 and TNF Play Different Roles in Various Models of Arthritis

| Arthritis Model | Species | Early Inflammation | | Erosive Arthritis | |
|-----------------|---------|--------------------|------|-------------------|------|
| | | TNF | IL-1 | TNF | IL-1 |
| SCW-A | Mouse | ++ | - | - | ++ |
| SCW-flare | Mouse | + | + | - | ++ |
| SCW-flare | Rat | + | + | | ++ |
| AIA | Mouse | ± | ± | | ++ |
| AIA | Rabbit | + | + | ± | ++ |
| AIA flare | Mouse | ± | + | - | ++ |
| CIA | Mouse | + | ++ | + | ++ |
| ICA | Mouse | - | ++ | - | ++ |
| AA | Rat | + | + | + | + |

See: W. van den Berg, Arthritis Res 3 (2001) 18-26

Collagen-Induced Arthritis: Anakinra and PEG sTNF-RI



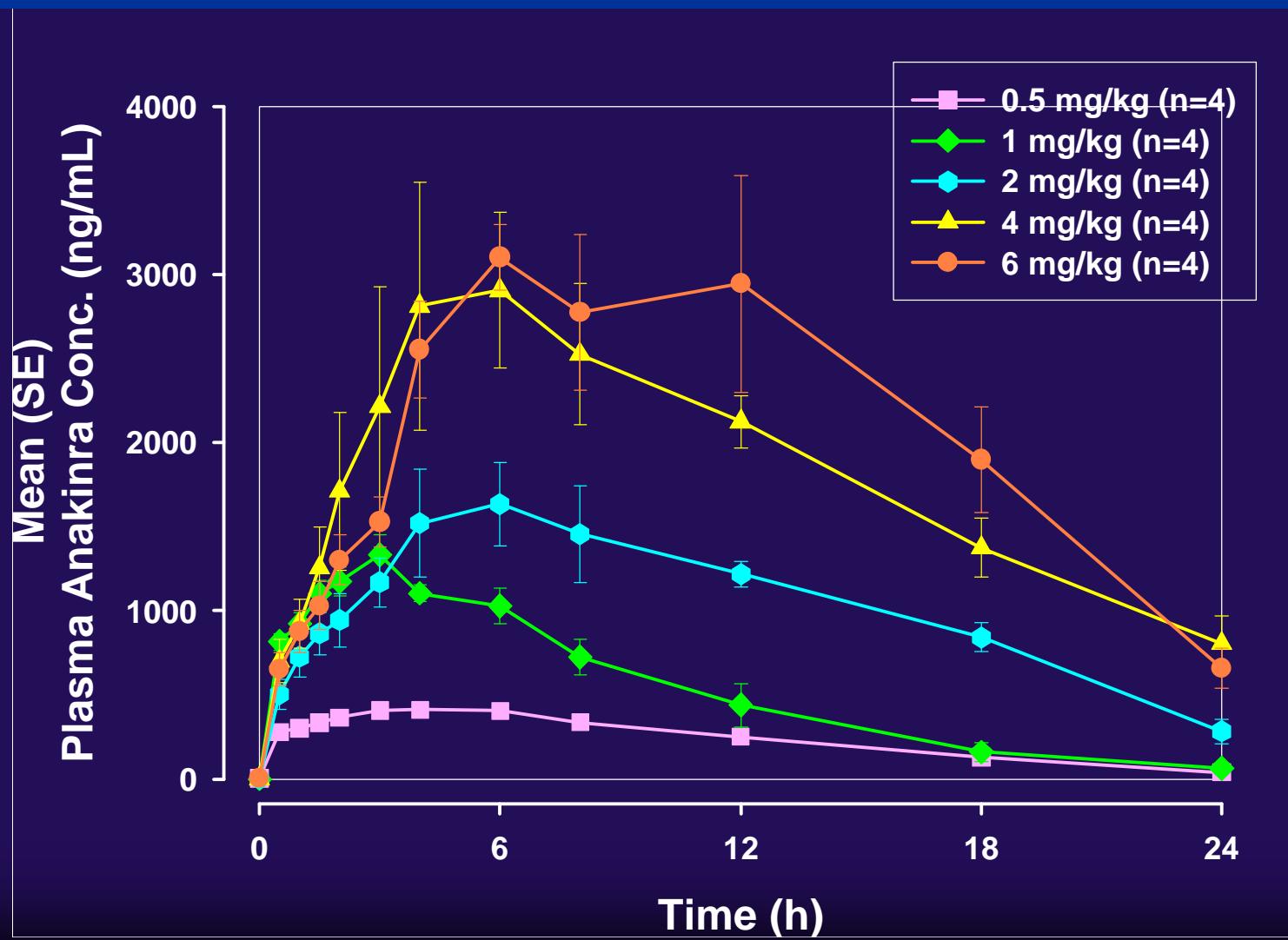
Development of Anakinra: Recombinant N-methionyl Human IL-1ra

- Gene isolated from IgG-stimulated human mononuclear phagocyte (monocyte) library (Eisenberg et al, 1990)
- Initial rDNA manufacturing process 1990
- Drug substance (active ingredient)
 - Recombinant protein
 - 153 amino acids
 - 17.3 kd
- Final dosage form
 - Daily injectable
 - 100 mg, fixed dose, prefilled syringes

Preclinical Safety Studies of Anakinra

- Toxicity of anakinra has been studied in rats and macaques
 - No neutralizing antibodies in studies up to 6-month duration
 - Safety margins exceeded 90-fold in rats and 30-fold in monkeys based on AUC
 - Tested alone and in combination with MTX, TNF inhibitors
- Animal studies have shown injection site inflammation, but no other target organ toxicity at any dose

Anakinra PK Profiles in RA Patients After SC Administration (Study 0501)



Regulatory Submissions

December 1999 License Application

0560

960180

960182

Selected Dose
100 mg/day

March 2001 Complete Response

990145

Efficacy and Safety

990757

Safety

Anakinra Rheumatoid Arthritis Patients

| | Number of Patients | |
|--|--------------------|----------|
| | Placebo | Anakinra |
| Randomized placebo-controlled studies and extensions | 759 | 2332 |
| Supportive studies | 3 | 199 |
| Pharmacokinetic studies | 15 | 75 |
| Total | 777 | 2606 |

Duration of Exposure in RA Patients

| Duration of Exposure | Number of Patients | |
|----------------------|--------------------------|-------|
| | All Anakinra ³ 100 mg | Doses |
| < 6 months | 484 | 795 |
| ≥ 6 months | 1379 | 1791 |
| ≥ 1 year | 237 | 551 |
| ≥ 2 years | 77 | 351 |
| ≥ 3 years | 26 | 160 |
| ≥ 4 years | 13 | 41 |
| ≥ 5 years | 5 | 19 |

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Randomized Placebo-Controlled Trials

| Study | Description | Daily Doses of Anakinra | N |
|--------|-----------------------------|-----------------------------------|------|
| 0560 | Monotherapy Study | 0, 30, 75, 150 mg | 472 |
| 960182 | Low Dose Monotherapy Study | 0, 2.5, 10, 30 mg | 141 |
| 960180 | MTX Combination Study | 0, 0.04, 0.1, 0.4, 1.0, 2.0 mg/kg | 419 |
| 990145 | Confirmatory Efficacy Study | 0, 100 mg | 501 |
| 990757 | Safety Study | 0, 100 mg | 1399 |
| | | Total | 2932 |

N = Number of subjects who received at least 1 dose of study drug.

RA Efficacy Trial Results

Earlier Efficacy Studies

0560

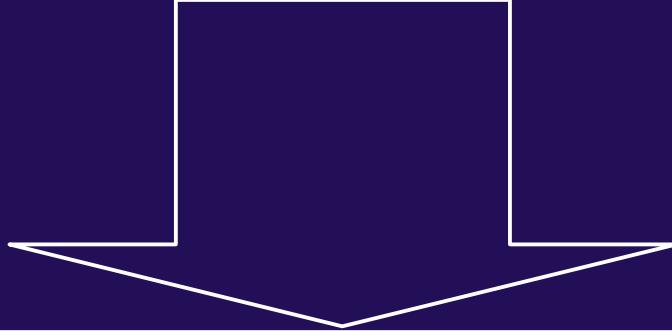
960182

960180

Signs & Symptoms
(150 mg/day)

Lower Doses Ineffective
(\leq 30 mg/day)

Signs & Symptoms
(1-2 mg/kg/day)



Study 990145

Confirms Signs and Symptoms Efficacy

100 mg/day

Patient Disposition

| | Study | | | | |
|----------------------------------|-------|--------|--------|--------|--------|
| | 0560 | 960182 | 960180 | 990145 | 990757 |
| Total randomized - n | 473 | 141 | 419 | 506 | 1414 |
| Never received drug - n | 1 | 0 | 0 | 5 | 15 |
| Completed - % | 72.9 | 87.9 | 79.0 | 75.7 | 78.1 |
| Withdrawn - % | 27.1 | 12.1 | 21.0 | 24.3 | 21.9 |
| Reason for withdrawal - % | | | | | |
| Adverse event | 17.3 | 5.7 | 7.2 | 10.9 | 10.4 |
| Lack of efficacy | 5.5 | 3.5 | 8.4 | 2.6 | 1.3 |
| Other | 4.2 | 2.8 | 5.5 | 10.9 | 9.9 |
| Death | 0.0 | 0.0 | 0.0 | 0.0 | 0.3 |

Baseline Demographics

| Mean | Study | | | | |
|----------------------|--------------------------|----------------------------|----------------------------|----------------------------|-----------------------------|
| | 0560 (N = 472) | 960182 (N = 141) | 960180 (N = 419) | 990145 (N = 501) | 990757 (N = 1399) |
| Female - % | 75.0 | 76.6 | 77.6 | 77.0 | 74.7 |
| Caucasian - % | 98.7 | 100.0 | 88.5 | 86.8 | 88.3 |
| Age (yr) | 53.1 | 52.2 | 52.5 | 56.3 | 54.8 |
| Weight (kg) | 69.6 | 70.1 | 78.6 | 81.1 | 76.8 |

Baseline Disease Status

| Mean | Study | | | | |
|--------------------------------|--------------------------|----------------------------|----------------------------|----------------------------|-----------------------------|
| | 0560 (N = 472) | 960182 (N = 141) | 960180 (N = 419) | 990145 (N = 501) | 990757 (N = 1399) |
| Duration of RA (yr) | 4.0 | 3.5 | 7.4 | 10.8 | 10.3 |
| Tender/Painful (0 - 68) | 34.3 | 33.0 | 25.4 | 25.6 | 22.6 |
| Swollen (0 - 66) | 26.1 | 23.7 | 18.3 | 20.0 | 18.7 |
| HAQ (0 - 3) | 1.57 | 1.64 | 1.40 | 1.34 | 1.41 |
| CRP (mg/dL) | 4.14 | 3.17 | 1.91 | 2.63 | 2.67 |
| ESR (mm/hr) | 49.5 | 43.2 | 36.7 | 42.2 | N/A |

Baseline RA Medications

| Use at Baseline - % | Study | | | | |
|---------------------------|-------------------|---------------------|---------------------|---------------------|----------------------|
| | 0560 (N = 472) | 960182 (N = 141) | 960180 (N = 419) | 990145 (N = 501) | 990757 (N = 1399) |
| Corticosteroid | 42.6 | 44.0 | 64.2 | 52.7 | 57.8 |
| NSAID | 83.5 | 85.8 | 69.0 | 76.4 | 87.0 |
| MTX Alone | 0 | 0 | 100 | 100 | 31.1 |
| Other DMARD Excluding MTX | 0 | 0 | 0 | 0 | 25.4 |
| MTX + Other DMARD | 0 | 0 | 0 | 0 | 22.3 |

Randomized Placebo-Controlled Trials

| Study | Description | N |
|--------|-----------------------------|------|
| 0560 | Monotherapy Study | 472 |
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| 990757 | Safety Study | 1399 |
| | Total | 2932 |

N = Number of subjects who received at least 1 dose of study drug.

Protocol 0560

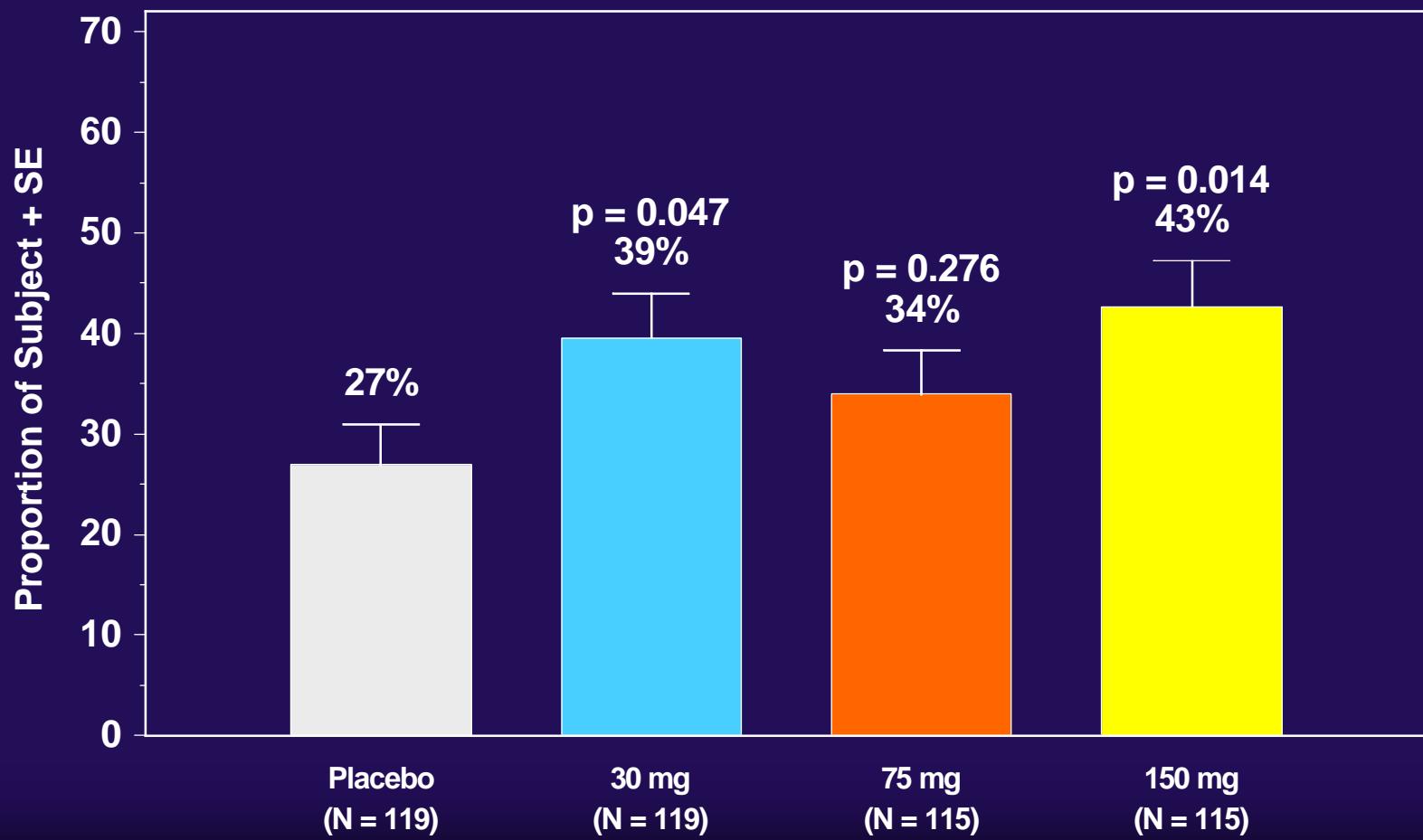
Monotherapy Study

| | |
|---------------------|--|
| Design: | Randomized, Blinded, Placebo-Controlled |
| Dosage: | 0, 30, 75, 150 mg daily SC No MTX or other DMARDs |
| Patients: | 472 |
| Duration: | 24 weeks |
| Location: | Europe |
| Primary endpoint: | ACR ₂₀ at 24 weeks |
| Secondary endpoint: | Larsen score at 24 weeks (Radiographic endpoint) |

Study 0560

Primary Endpoint: ACR₂₀ at Week 24

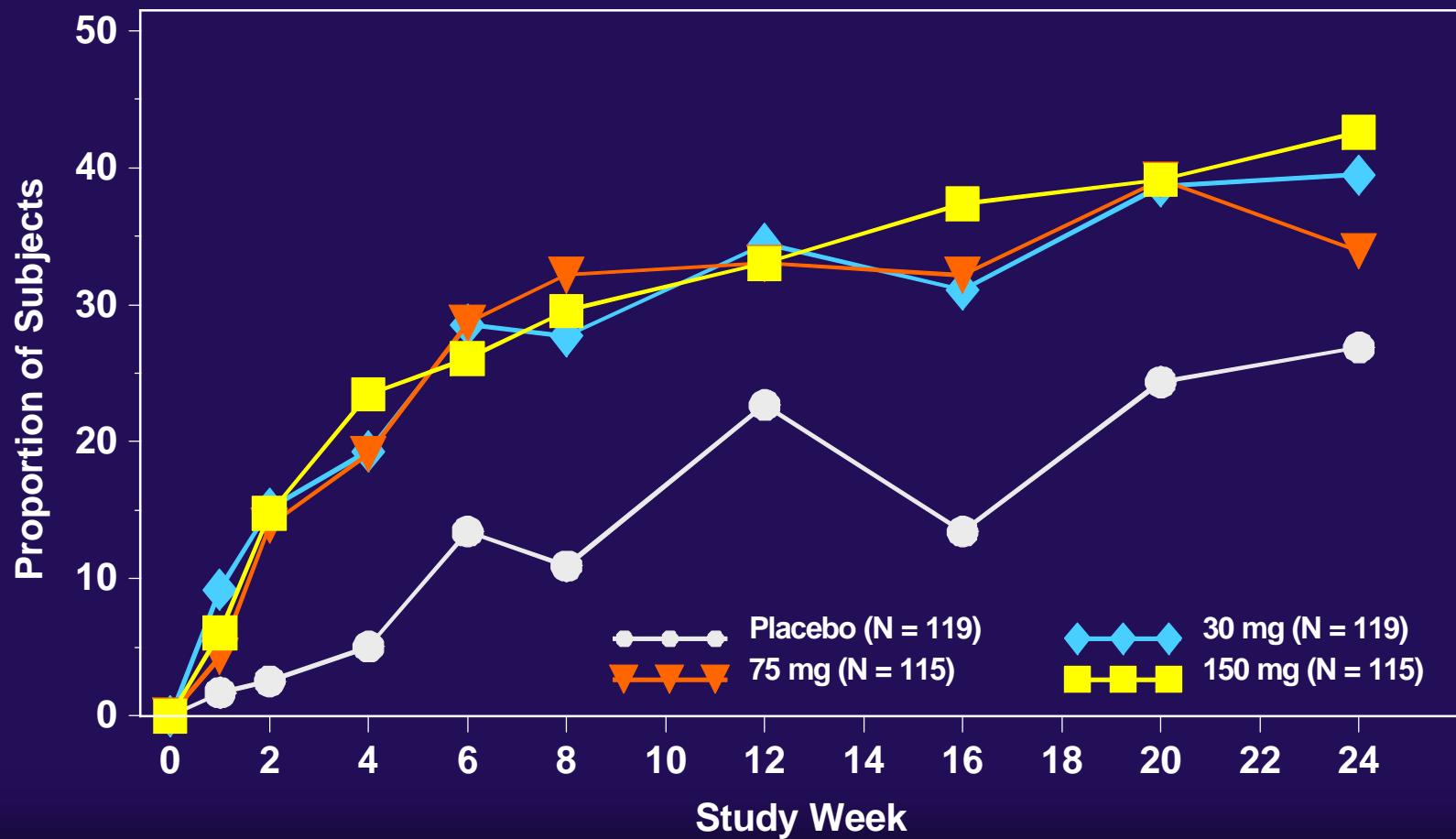
M-ITT LOCF Imputation



Study 0560

ACR₂₀ Response by Study Week

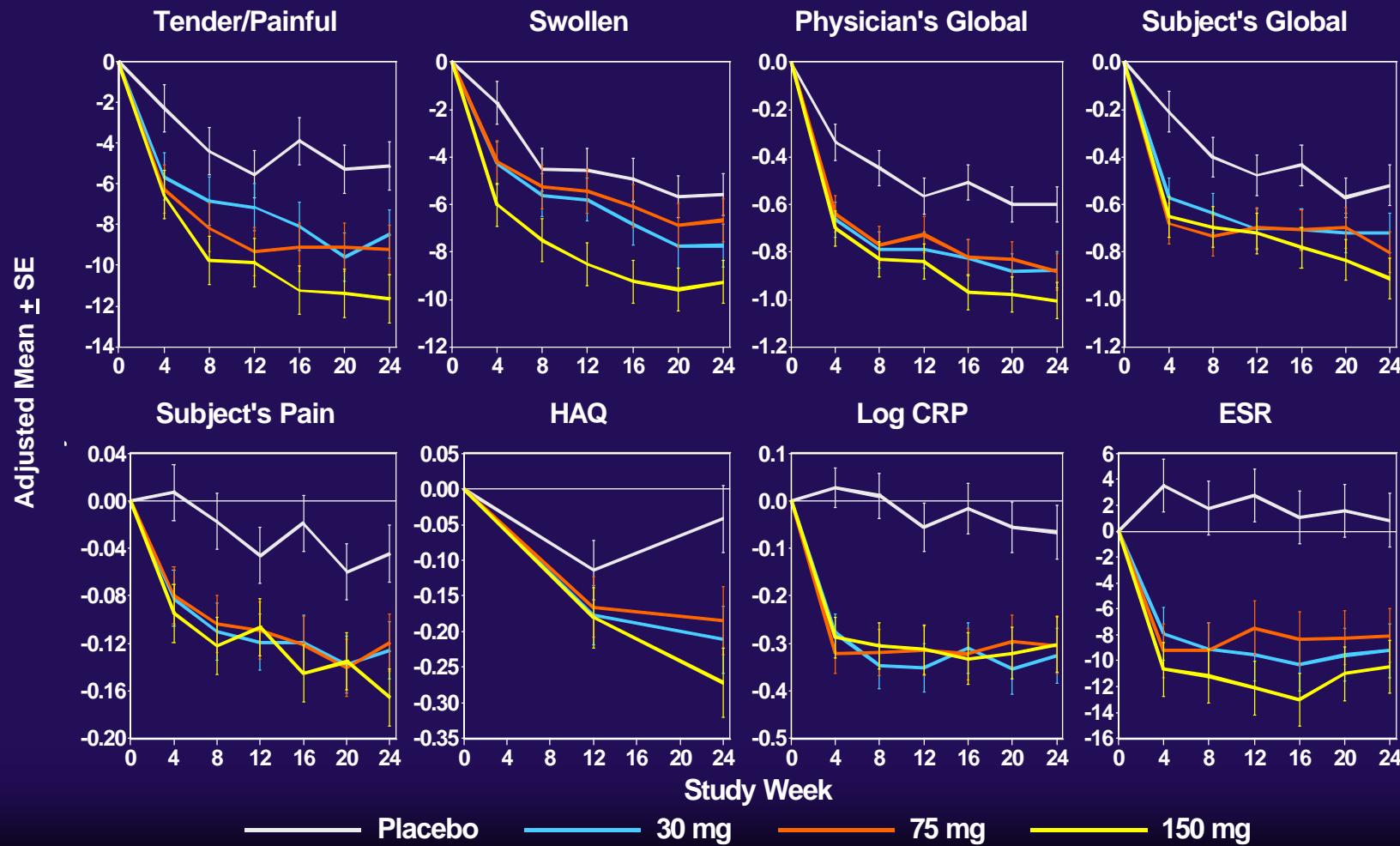
M-ITT LOCF Imputation



Study 0560

Individual ACR Components by Study Week

Change From Baseline (M-ITT LOCF Repeated Measures Mixed Model)



Study 0560

Summary of Results

- Effective in reducing signs and symptoms of RA
 - In a monotherapy setting

Randomized Placebo-Controlled Trials

| Study | Description | N |
|--------|-----------------------------|------|
| 0560 | Monotherapy Study | 472 |
| 960182 | Low Dose Monotherapy Study | 141 |
| 960180 | MTX Combination Study | 419 |
| 990145 | Confirmatory Efficacy Study | 501 |
| 990757 | Safety Study | 1399 |
| | Total | 2932 |

N = Number of subjects who received at least 1 dose of study drug.

Protocol 960182

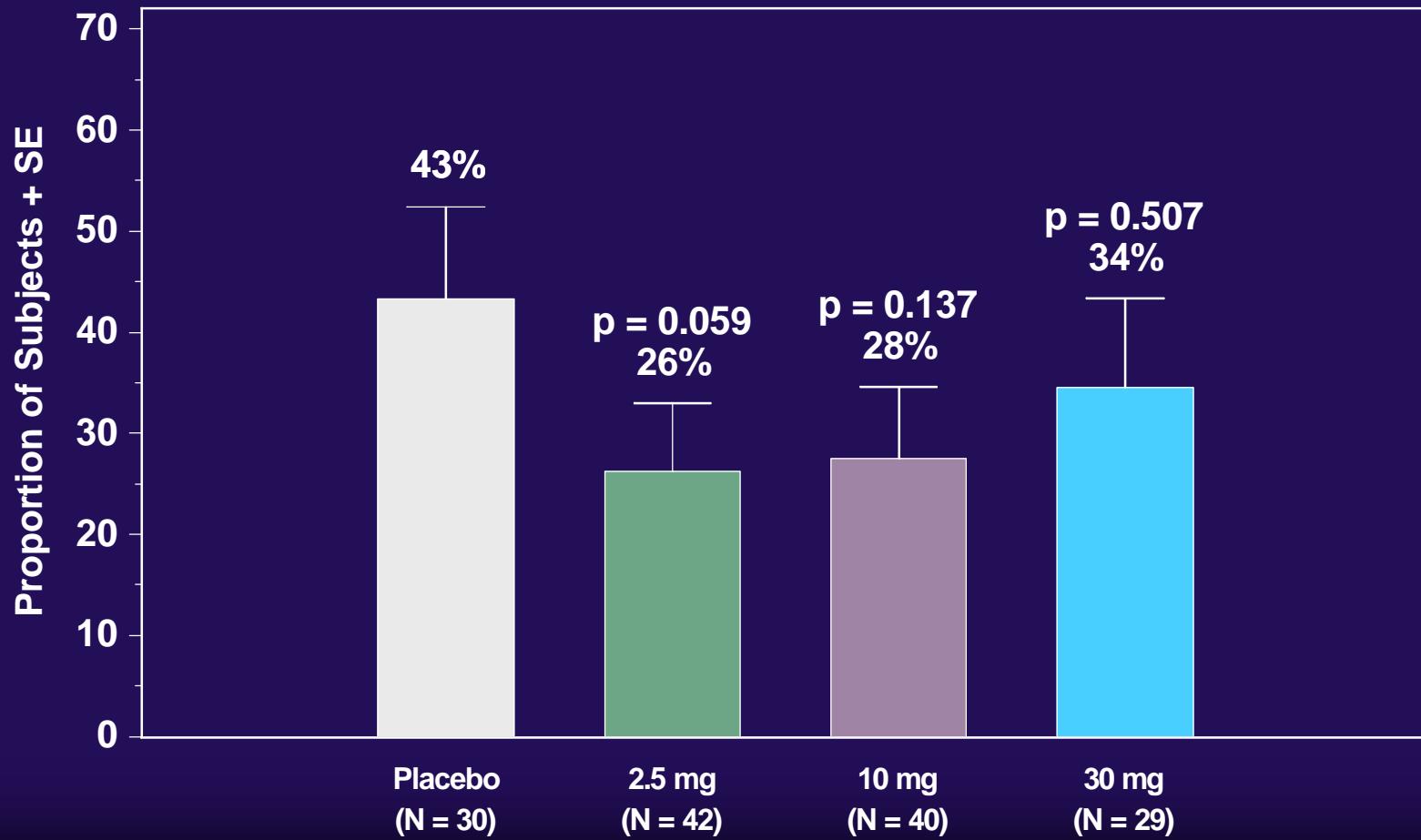
Low Dose Monotherapy Study

| | |
|-------------------|--|
| Design: | Randomized, Blinded, Placebo-Controlled |
| Dosage: | 0, 2.5, 10, 30 mg daily SC No MTX or other DMARDs |
| Patients: | 141 |
| Duration: | 12 weeks |
| Location: | Europe |
| Primary endpoint: | ACR ₂₀ at 12 weeks |

Study 960182

Primary Endpoint: ACR₂₀ at Week 12

ITT Nonresponder Imputation



Study 960182

Summary of Results

- Signs and symptoms endpoint not achieved
 - Doses \leq 30 mg not effective
 - Small sample size and low statistical power
 - Greater than expected placebo response rate

Randomized Placebo-Controlled Trials

| Study | Description | N |
|--------|-----------------------------|------|
| 0560 | Monotherapy Study | 472 |
| 960182 | Low Dose Monotherapy Study | 141 |
| 960180 | MTX Combination Study | 419 |
| 990145 | Confirmatory Efficacy Study | 501 |
| 990757 | Safety Study | 1399 |
| | Total | 2932 |

N = Number of subjects who received at least 1 dose of study drug.

Protocol 960180

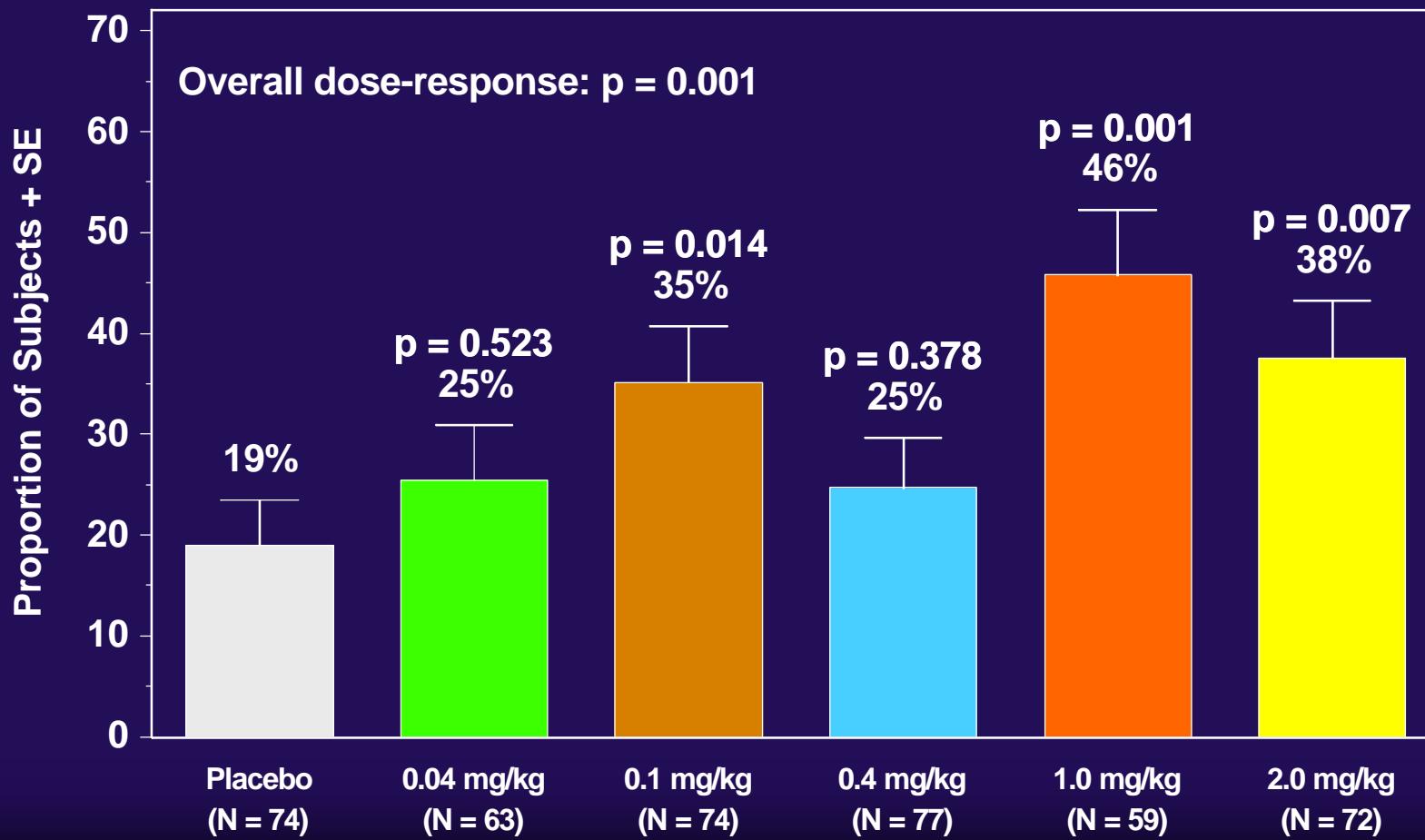
MTX Combination Study

| | |
|---------------------|--|
| Design: | Randomized, Blinded, Placebo-Controlled |
| Dosage: | 0, 0.04, 0.1, 0.4, 1.0, 2.0 mg/kg daily SC MTX background (15 - 25 mg/wk) |
| Patients: | 419 |
| Duration: | 12 weeks, amended to 24 weeks |
| Location: | US, Canada, Australia |
| Primary endpoint: | ACR ₂₀ at 12 weeks |
| Secondary endpoint: | ACR ₂₀ at 24 weeks |

Study 960180

Primary Endpoint: ACR₂₀ at Week 12

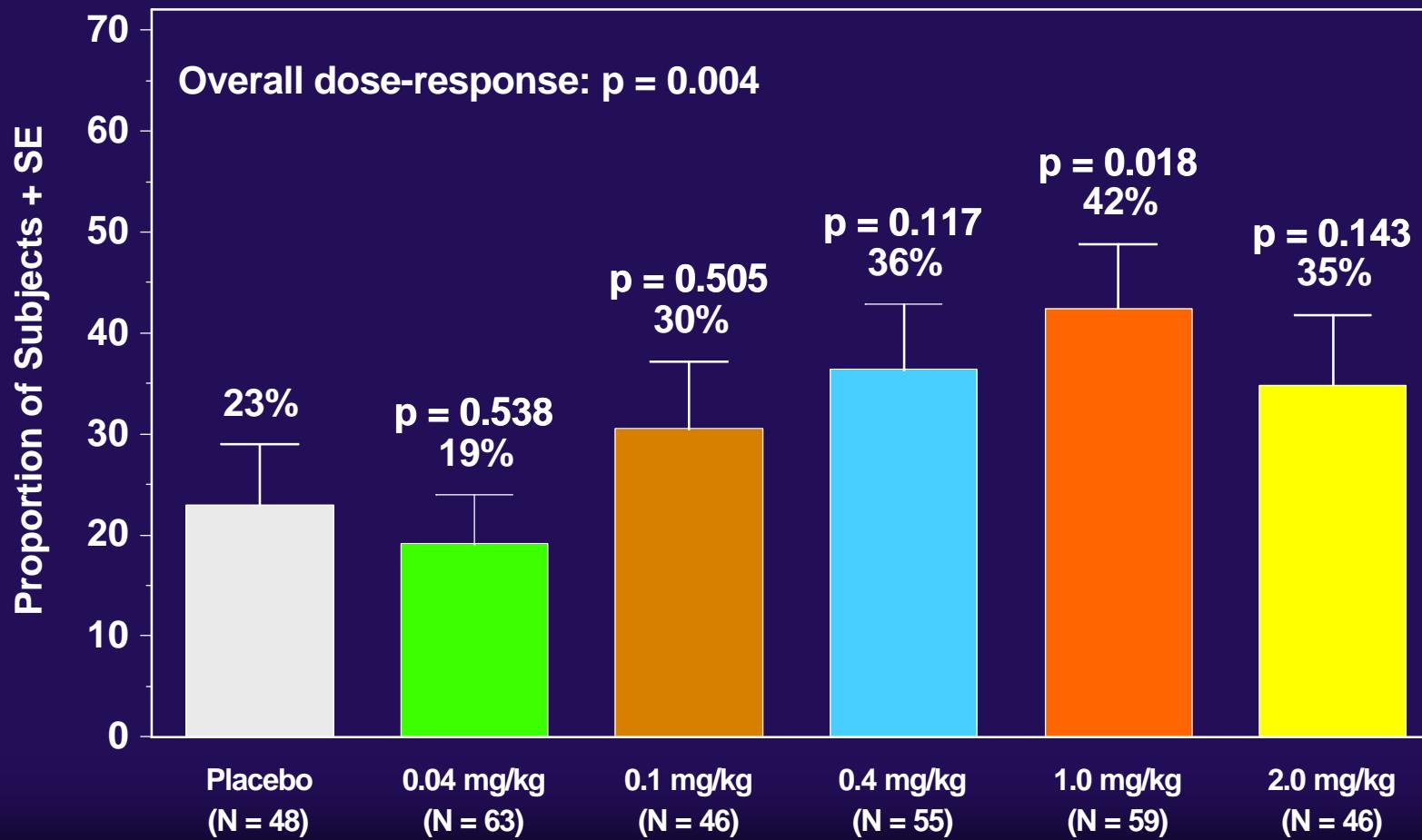
ITT Nonresponder Imputation



Study 960180

Secondary Endpoint: ACR₂₀ at Week 24

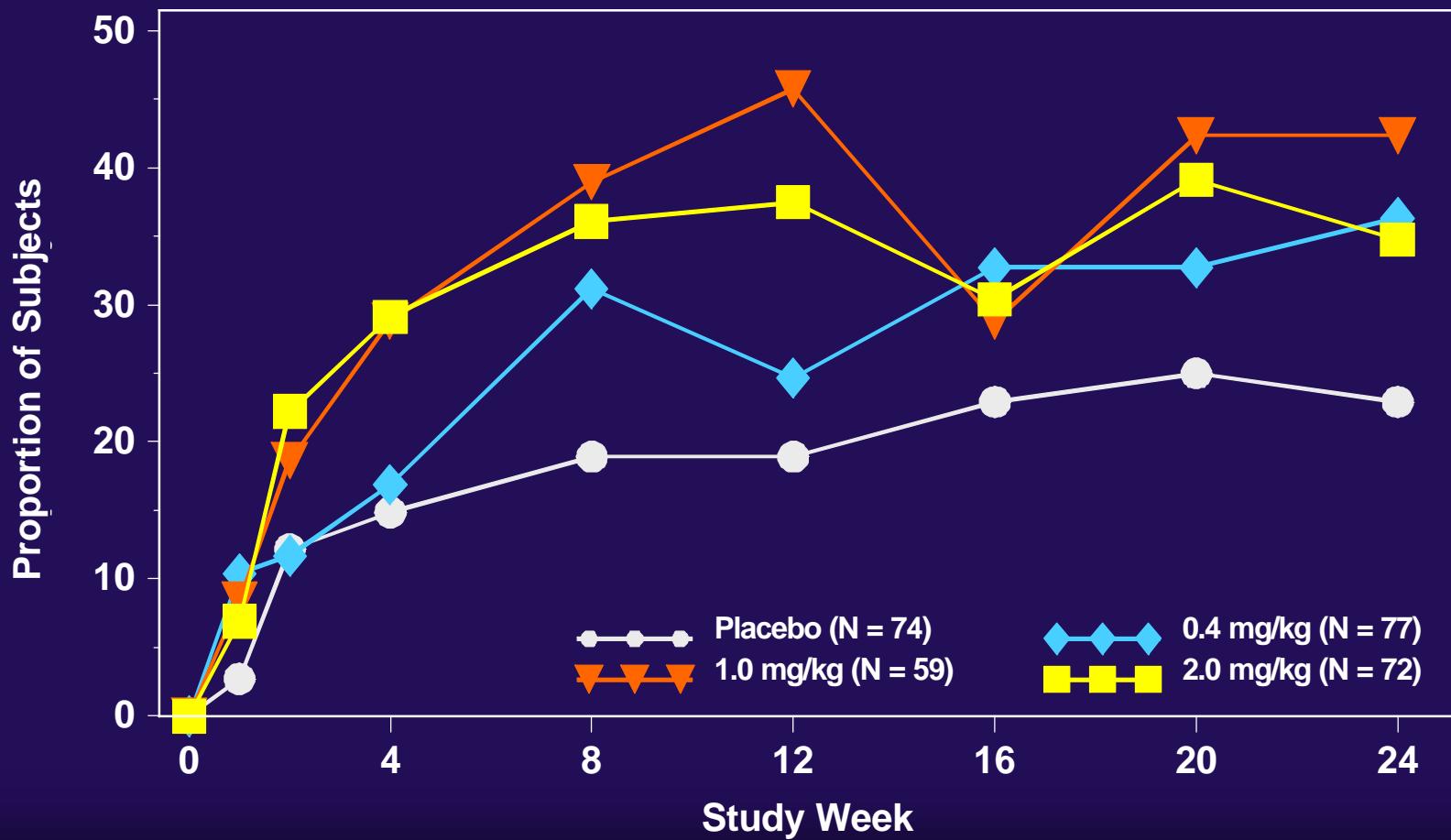
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Study 960180

ACR₂₀ Response by Study Week

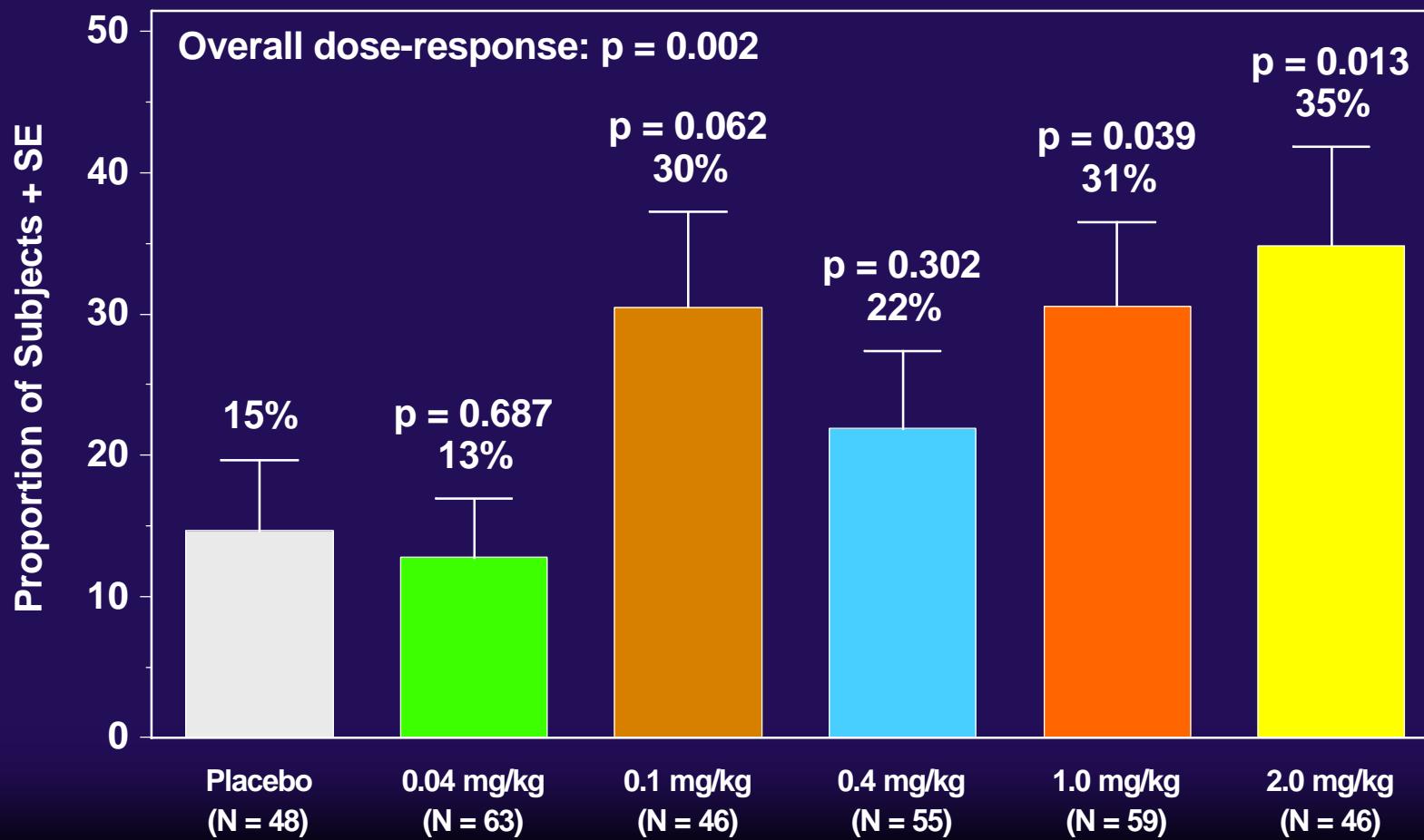
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Study 960180

Sustained ACR₂₀ Response

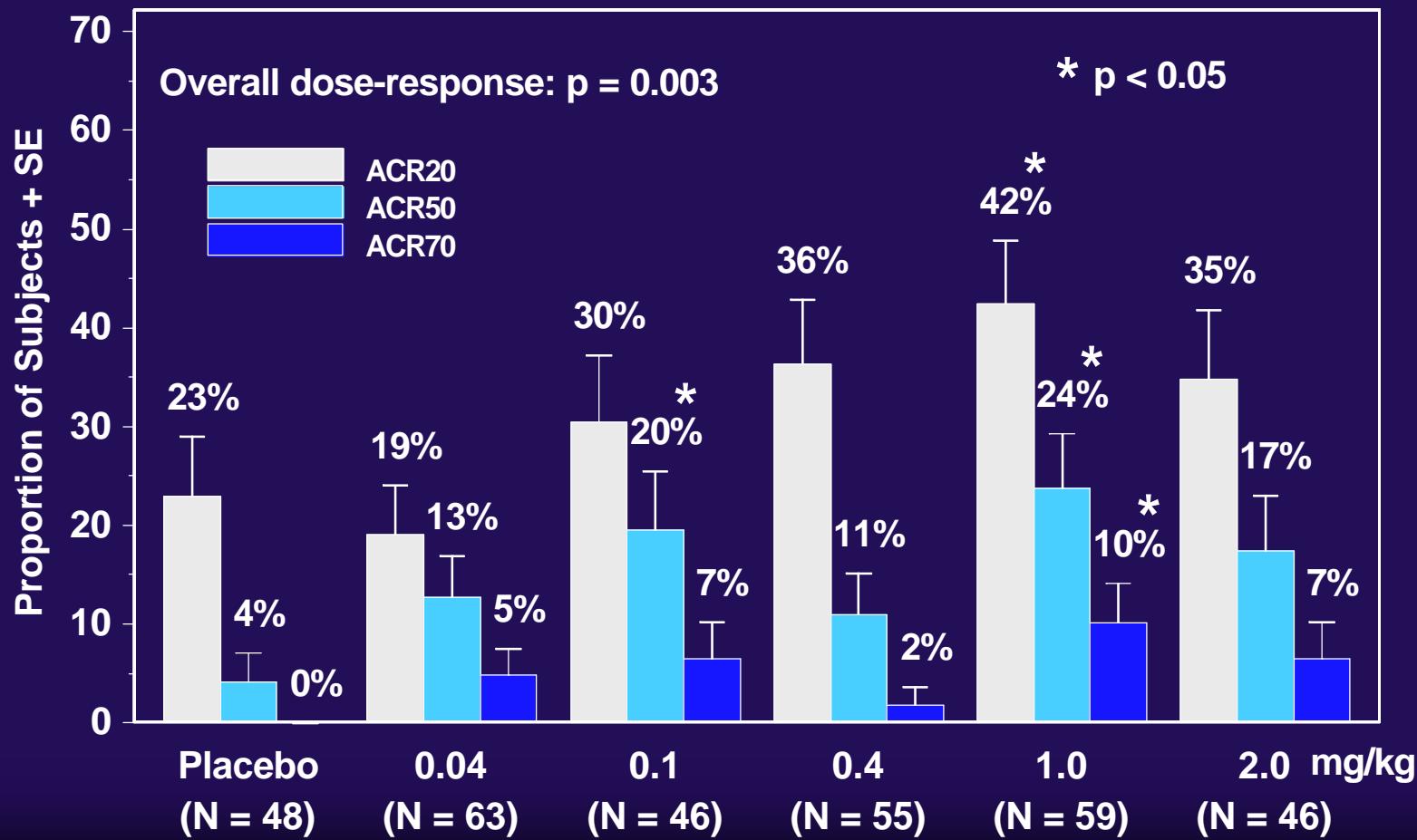
Response for at Least 4 of 6 Months
ITT Nonresponder Imputation



Study 960180

ACR₂₀, ACR₅₀, and ACR₇₀ at Week 24

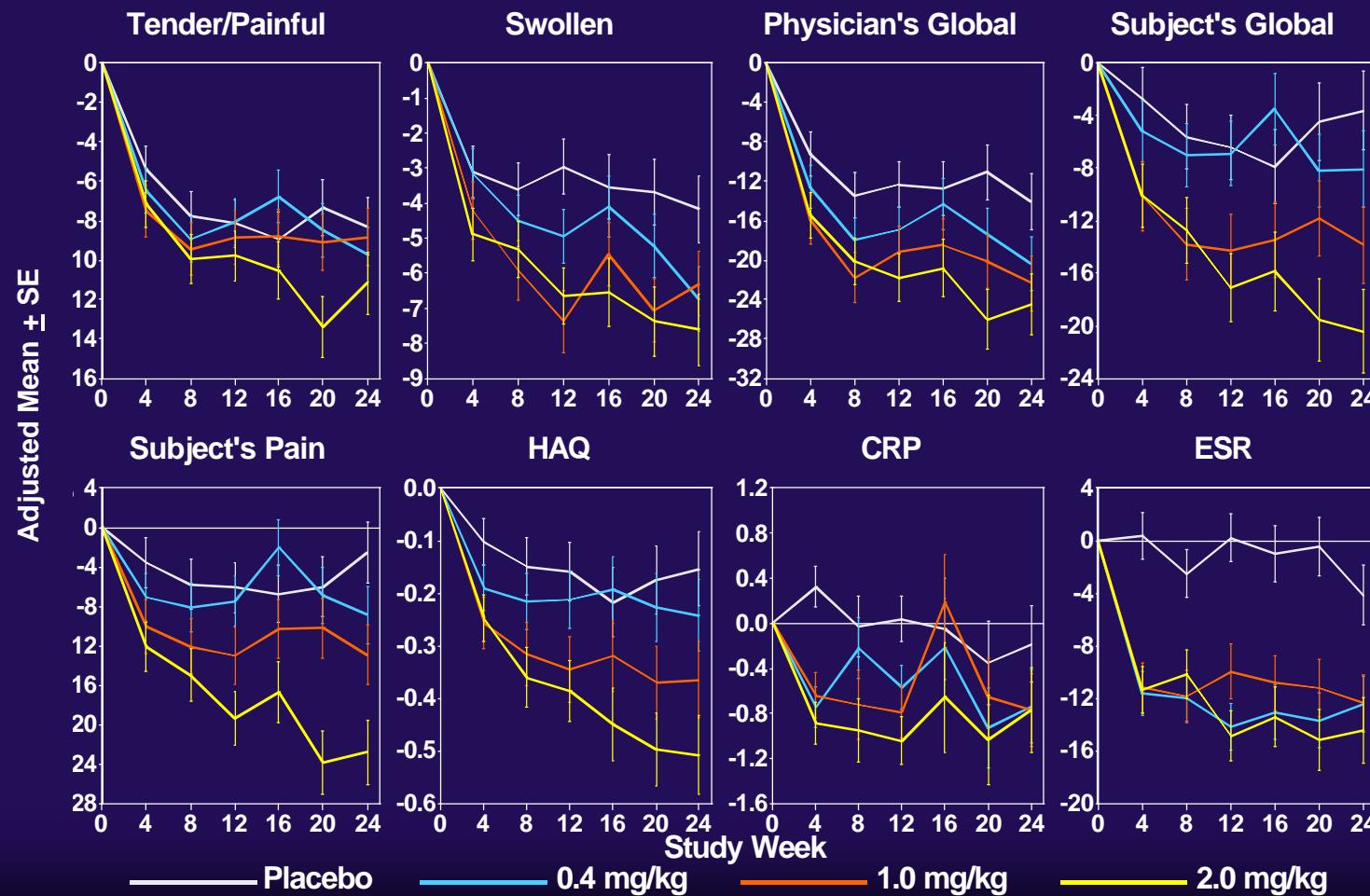
ITT Nonresponder Imputation



Study 960180

Individual ACR Components by Study Week

Change From Baseline (ITT Repeated Measures Mixed Model)



Study 960180

Summary of Results

- Effective in reducing signs and symptoms of RA
 - In combination with MTX

Randomized Placebo-Controlled Trials

| Study | Description | N |
|--------|-----------------------------|------|
| 0560 | Monotherapy Study | 472 |
| 960182 | Low Dose Monotherapy Study | 141 |
| 960180 | MTX Combination Study | 419 |
| 990145 | Confirmatory Efficacy Study | 501 |
| 990757 | Safety Study | 1399 |
| | Total | 2932 |

N = Number of subjects who received at least 1 dose of study drug.

Protocol 990145

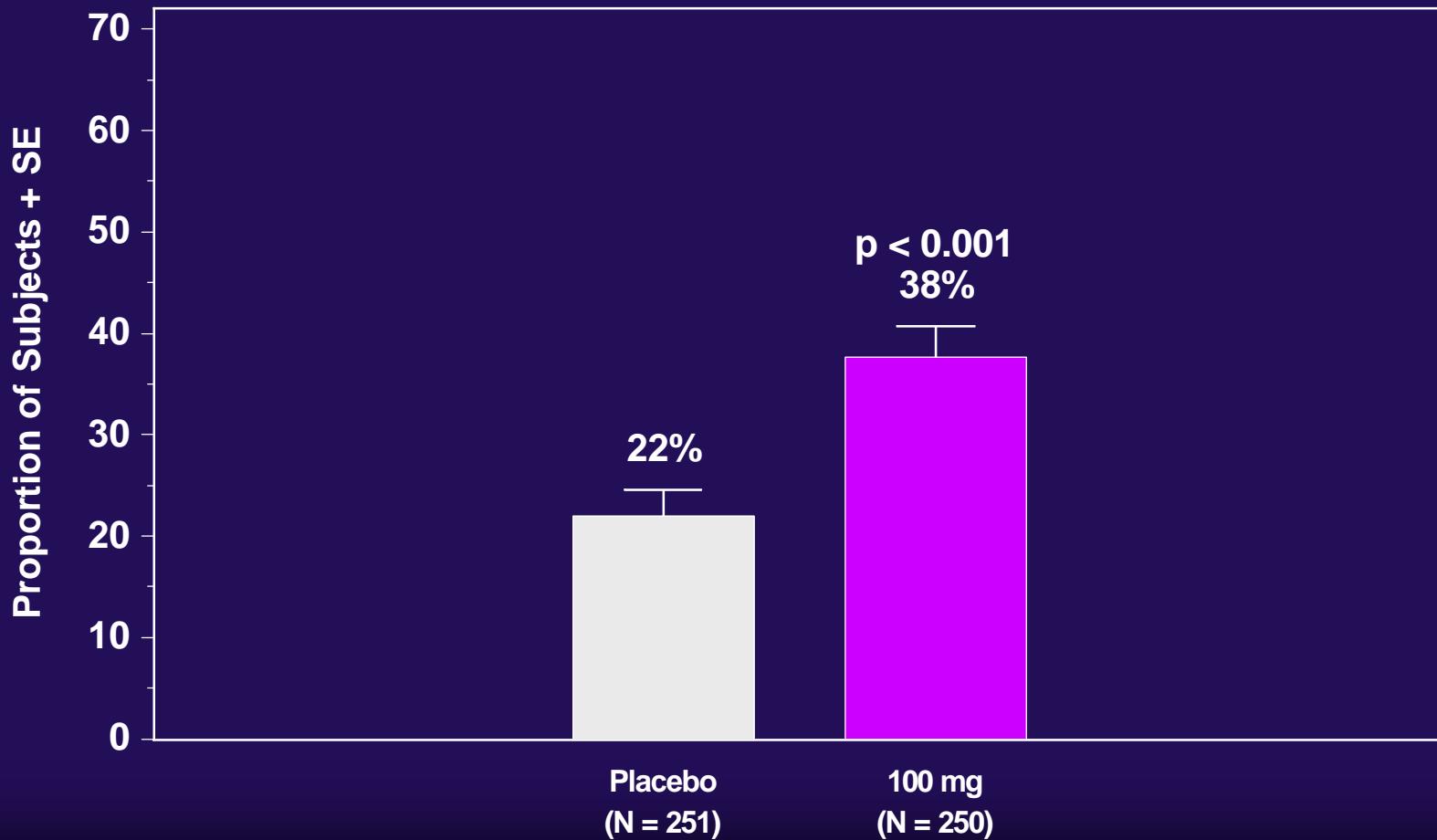
Confirmatory Efficacy Study

| | |
|---------------------|--|
| Design: | Randomized, Blinded, Placebo-Controlled |
| Dosage: | 0, 100 mg daily SC MTX background (10 - 25 mg/wk) |
| Patients: | 906 |
| Duration: | 52 weeks |
| Location: | US, Canada, Australia |
| Primary endpoint: | Sharp scores at week 52 |
| Signs and symptoms: | ACR ₂₀ at week 24 (N = 501) |

Study 990145

Signs and Symptoms—ACR₂₀ at Week 24

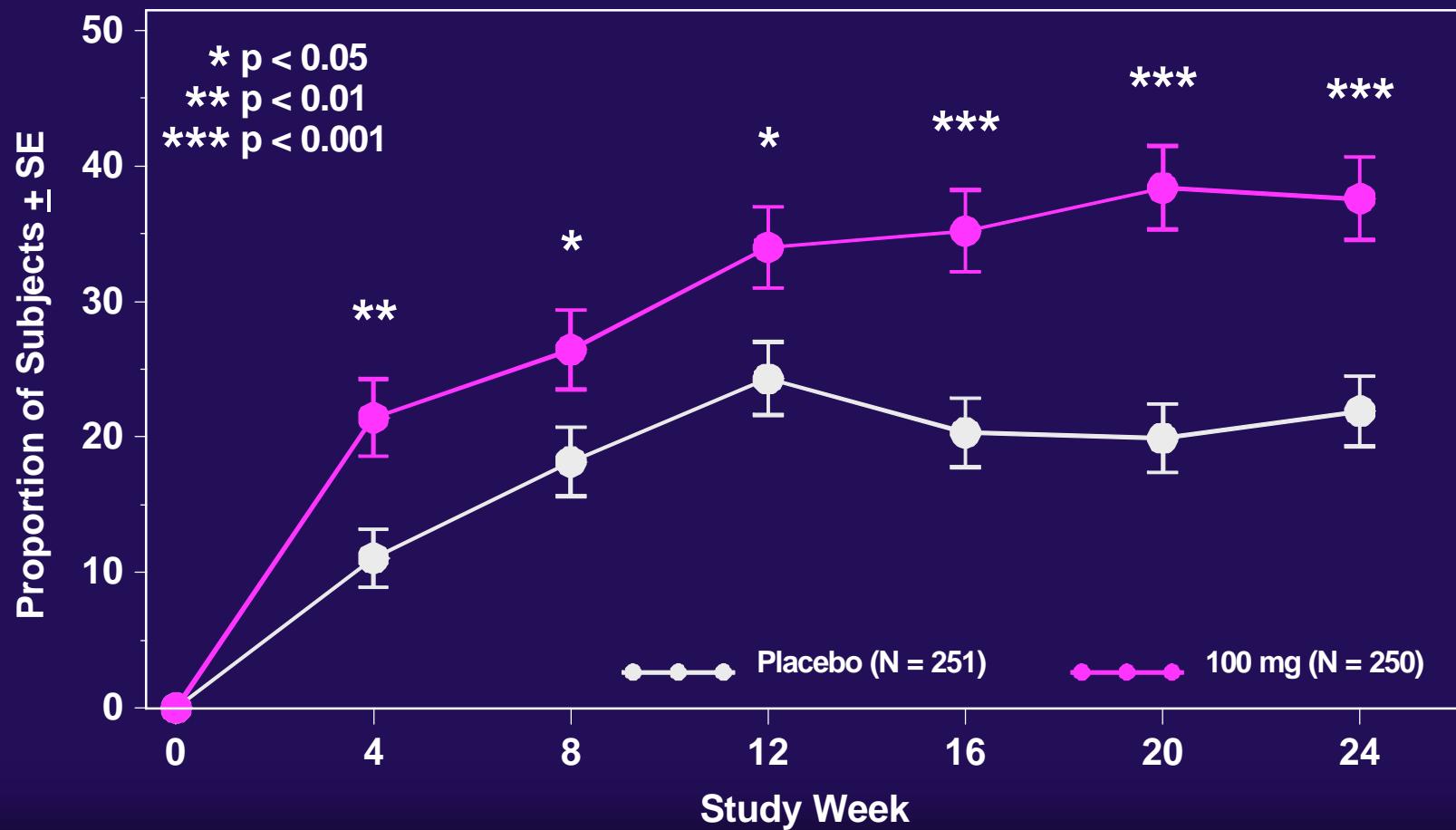
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Study 990145

ACR₂₀ Response by Study Week

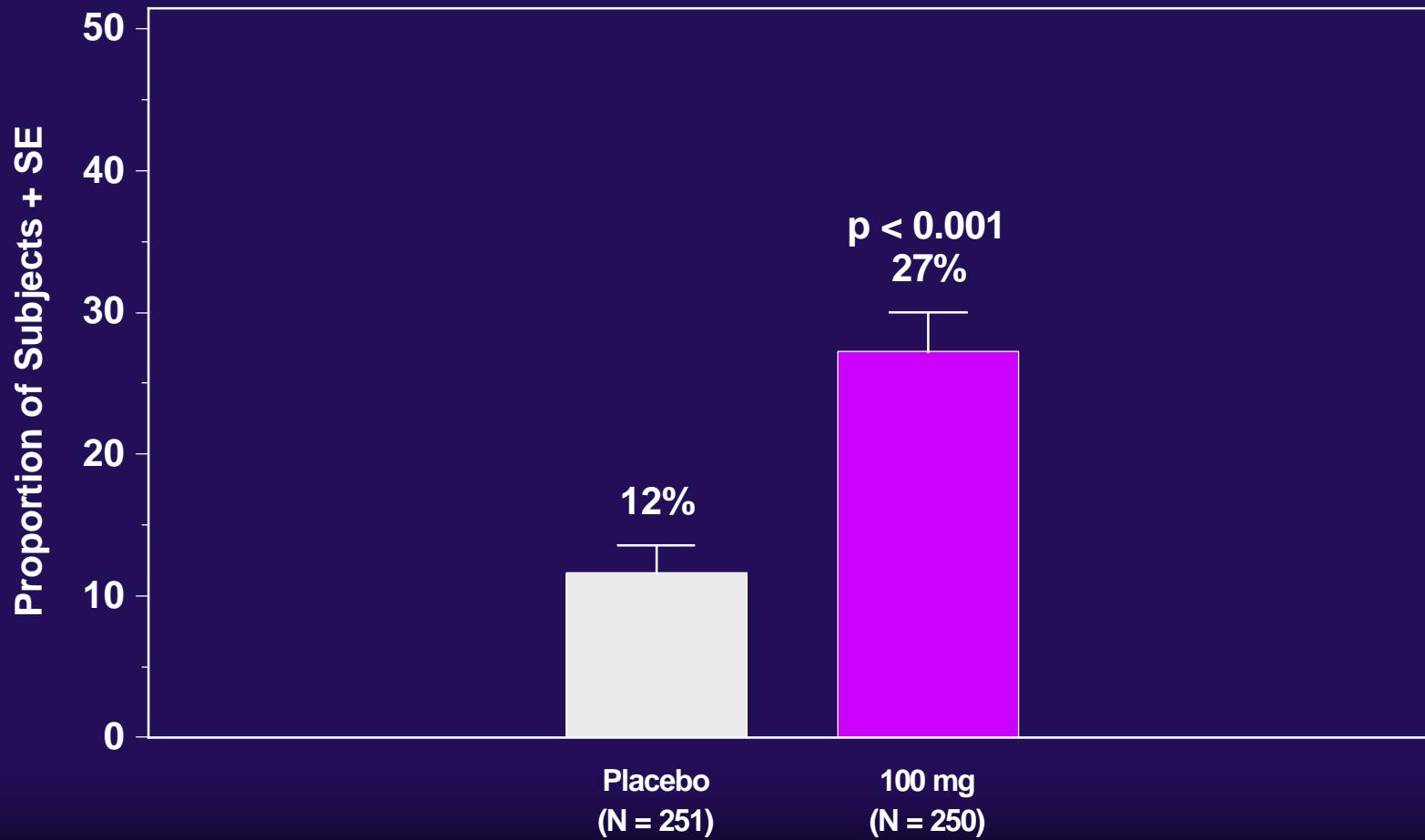
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Study 990145

Sustained ACR₂₀ Response

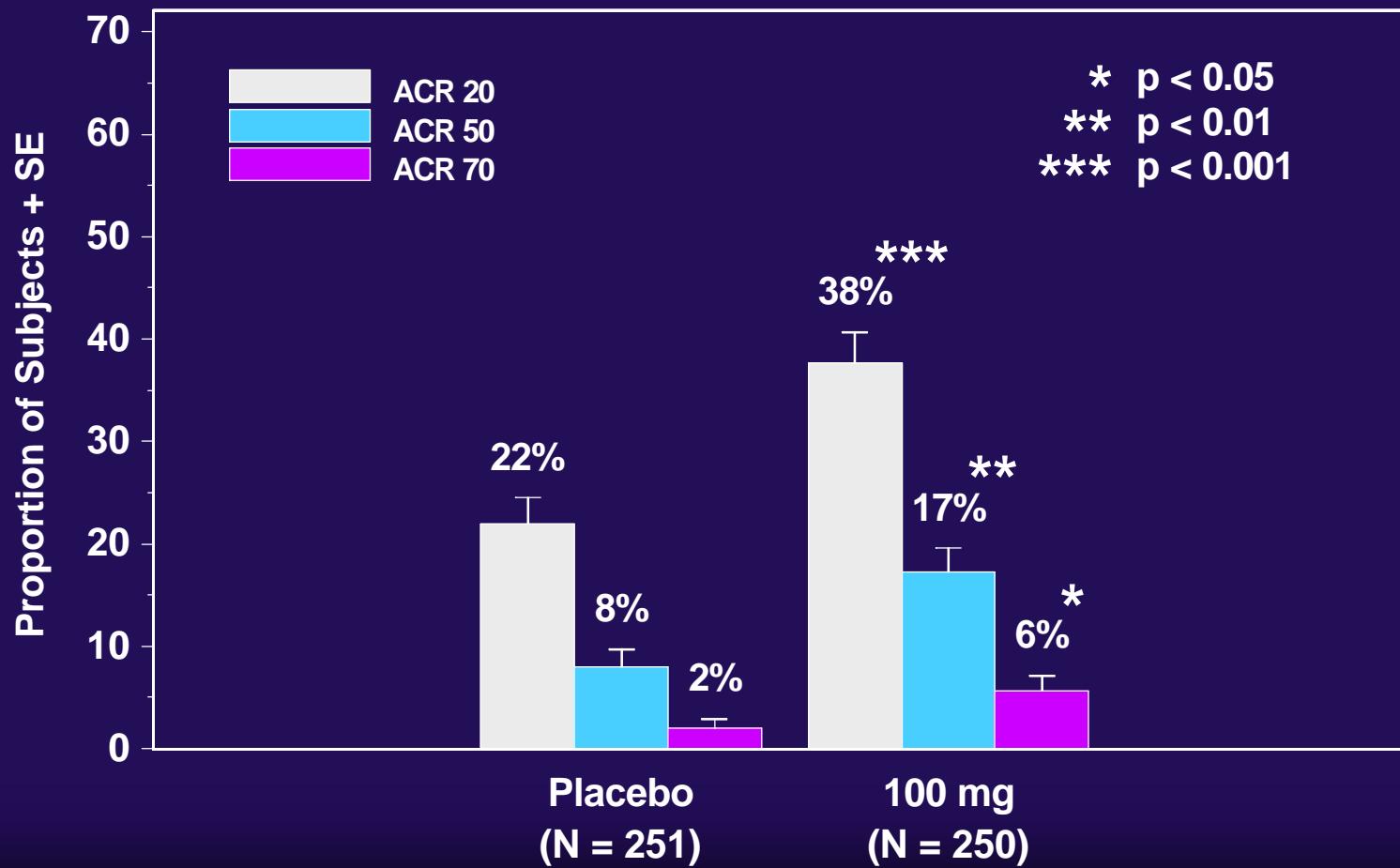
Response for at Least 4 of 6 Months
ITT Nonresponder Imputation



Study 990145

ACR₂₀, ACR₅₀, and ACR₇₀ at Week 24

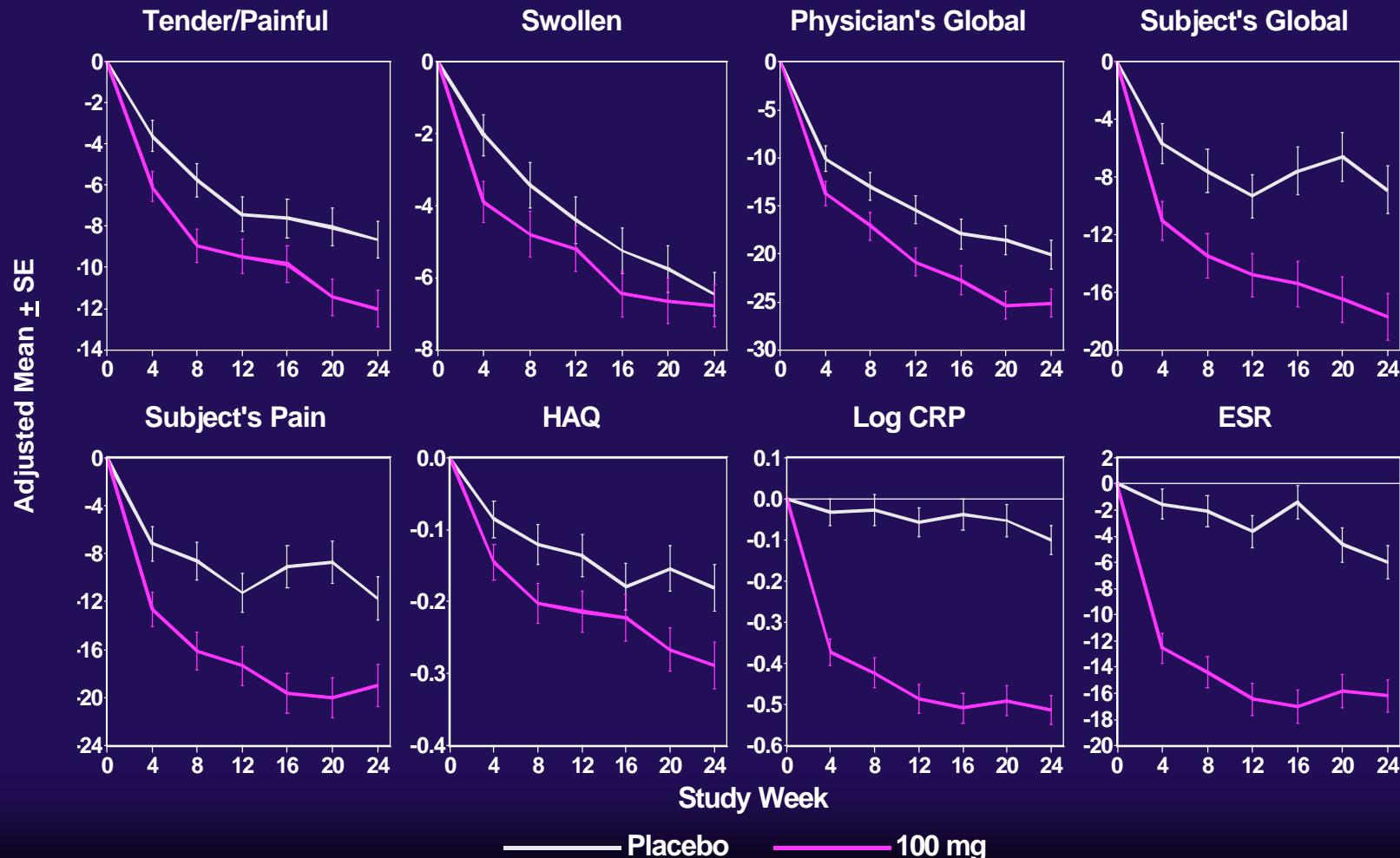
ITT Nonresponder Imputation



Study 990145

Individual ACR Components by Study Week

Change From Baseline (ITT Repeated Measures Mixed Model)



Study 990145

Summary of Results

- Confirms Efficacy: Signs and Symptoms of RA
 - ACR₂₀ response at 24 weeks
 - Early onset of action
 - Sustained ACR₂₀ response
 - Magnitude of response: ACR₅₀ and ACR₇₀
 - Components of ACR

Efficacy Data

Radiographic Endpoints – 24 Weeks

Study 0560

Study 0560

Radiographic Methods

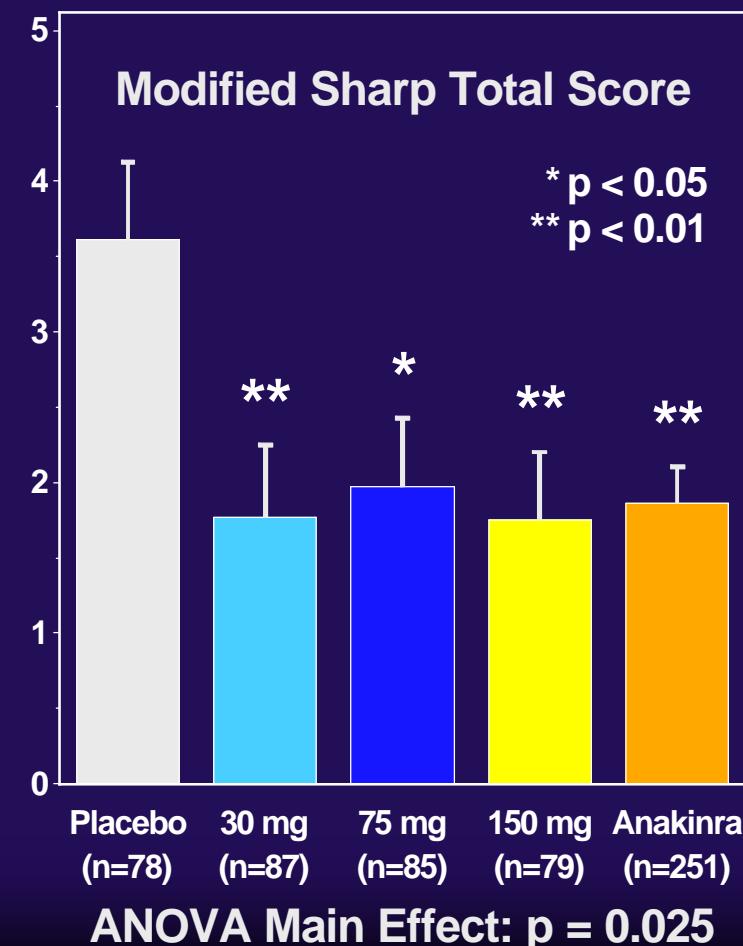
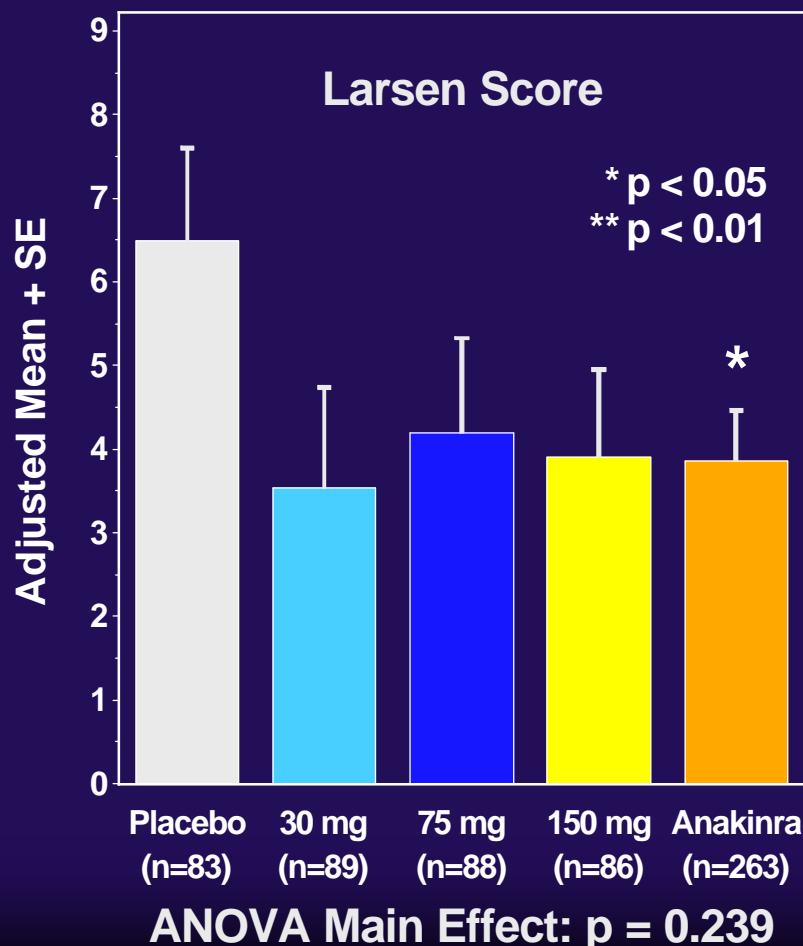
Two Independent Validated Methods

| | |
|----------------------------------|-----------------------------|
| Larsen Score | Genant Modified Sharp Score |
| Radiologists | Radiologist |
| Dr. Iain Watt Dr. Mark Cobley | Dr. Harry Genant |

Study 0560

Larsen and Modified Sharp Total Scores

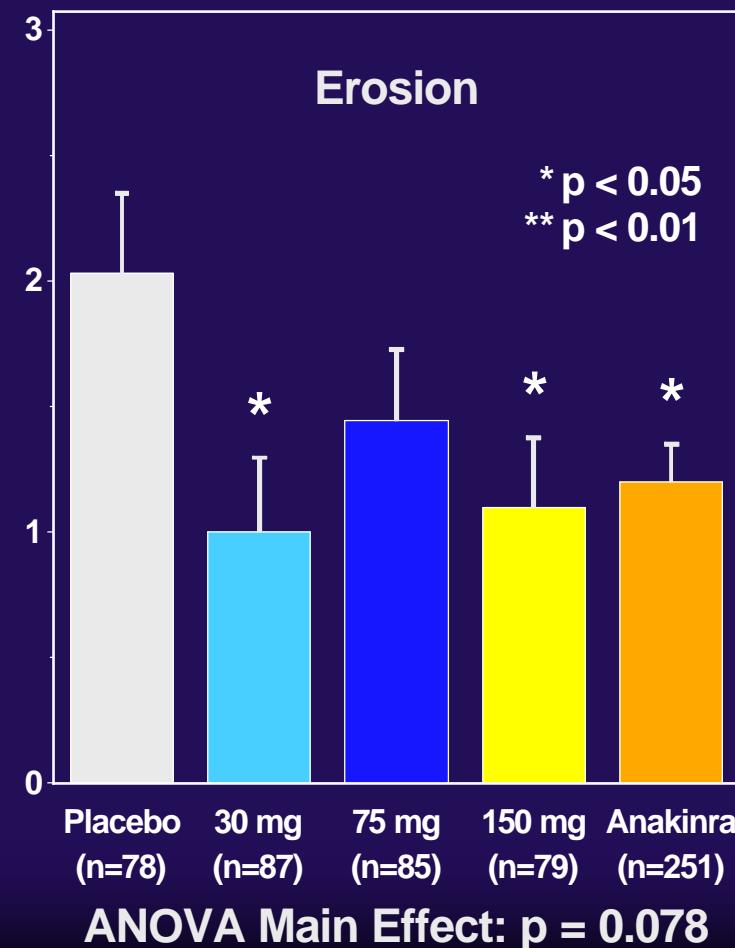
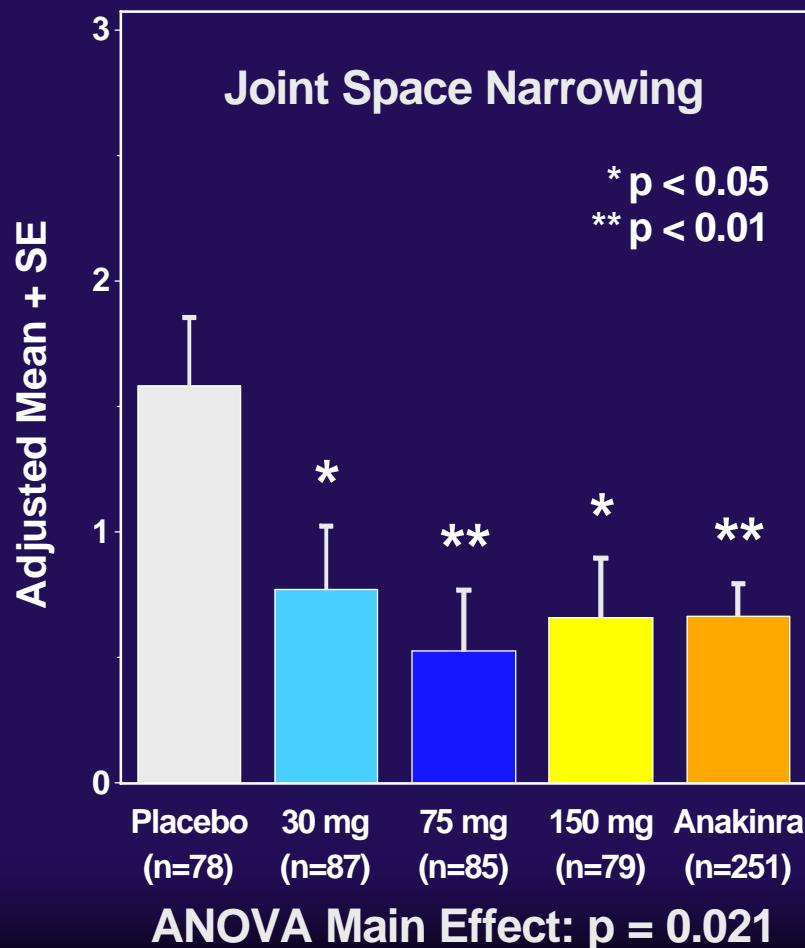
24-week Change From Baseline



Study 0560

Modified Sharp Score: Sub-scales

24-week Change From Baseline



Efficacy Data

Radiographic Endpoints – 48 Weeks

Studies 0560/0564

Studies 0560 and 0564

Study Schema

Study 0560

Weeks 1 to 24

R
A
N
D
O
M
I
Z
E
D

Placebo
N = 121

30 mg
N = 119

75 mg
N = 116

150 mg
N = 116

Study 0564

Weeks 24 to 48

C
O
M
P
L
E
T
E
R
S

Randomized

30 mg
N = 81

75 mg
N = 79

150 mg
N = 73

30 mg
N = 30

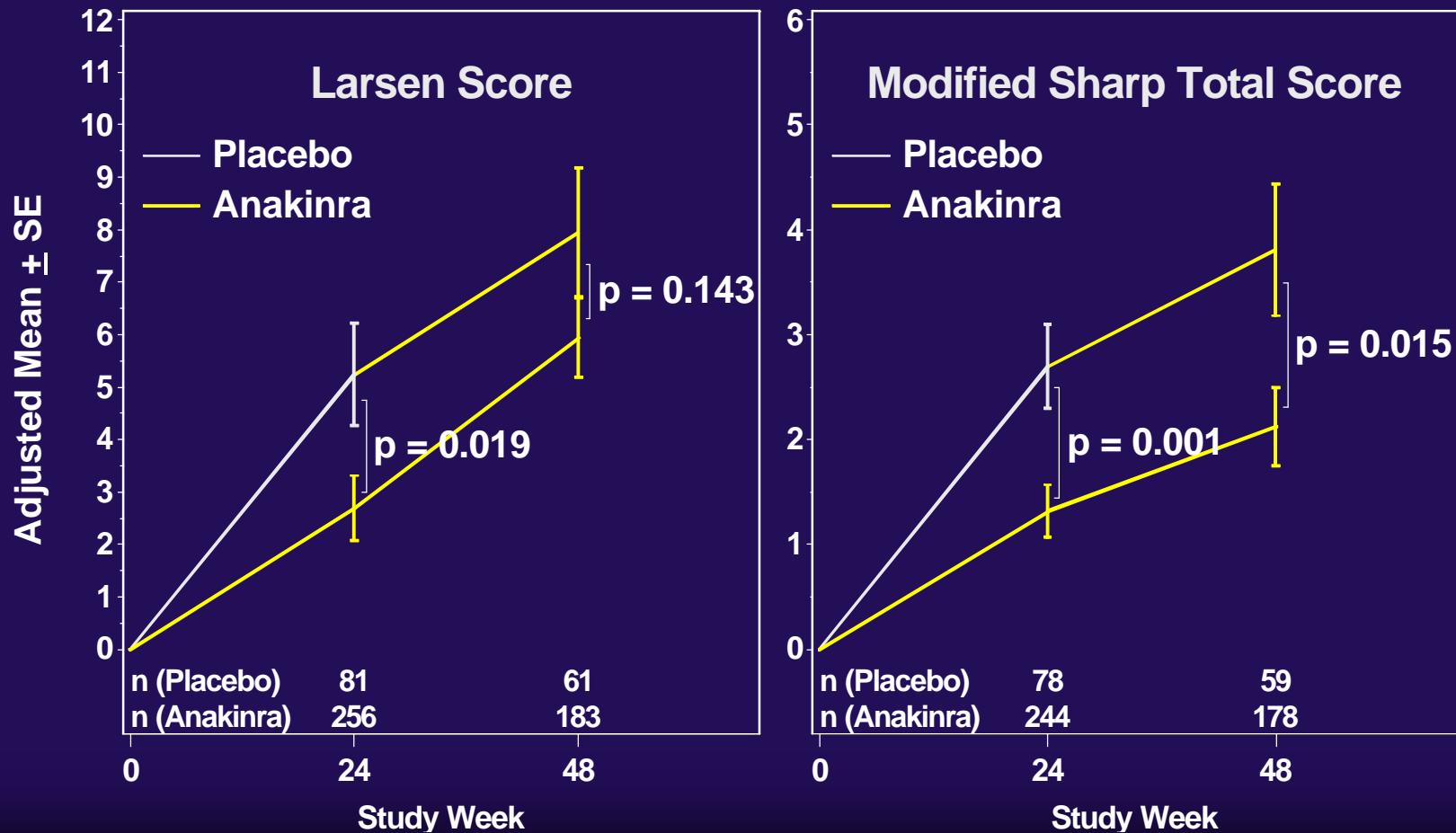
75 mg
N = 24

150 mg
N = 22

Studies 0560 and 0564

Larsen and Modified Sharp Total Score

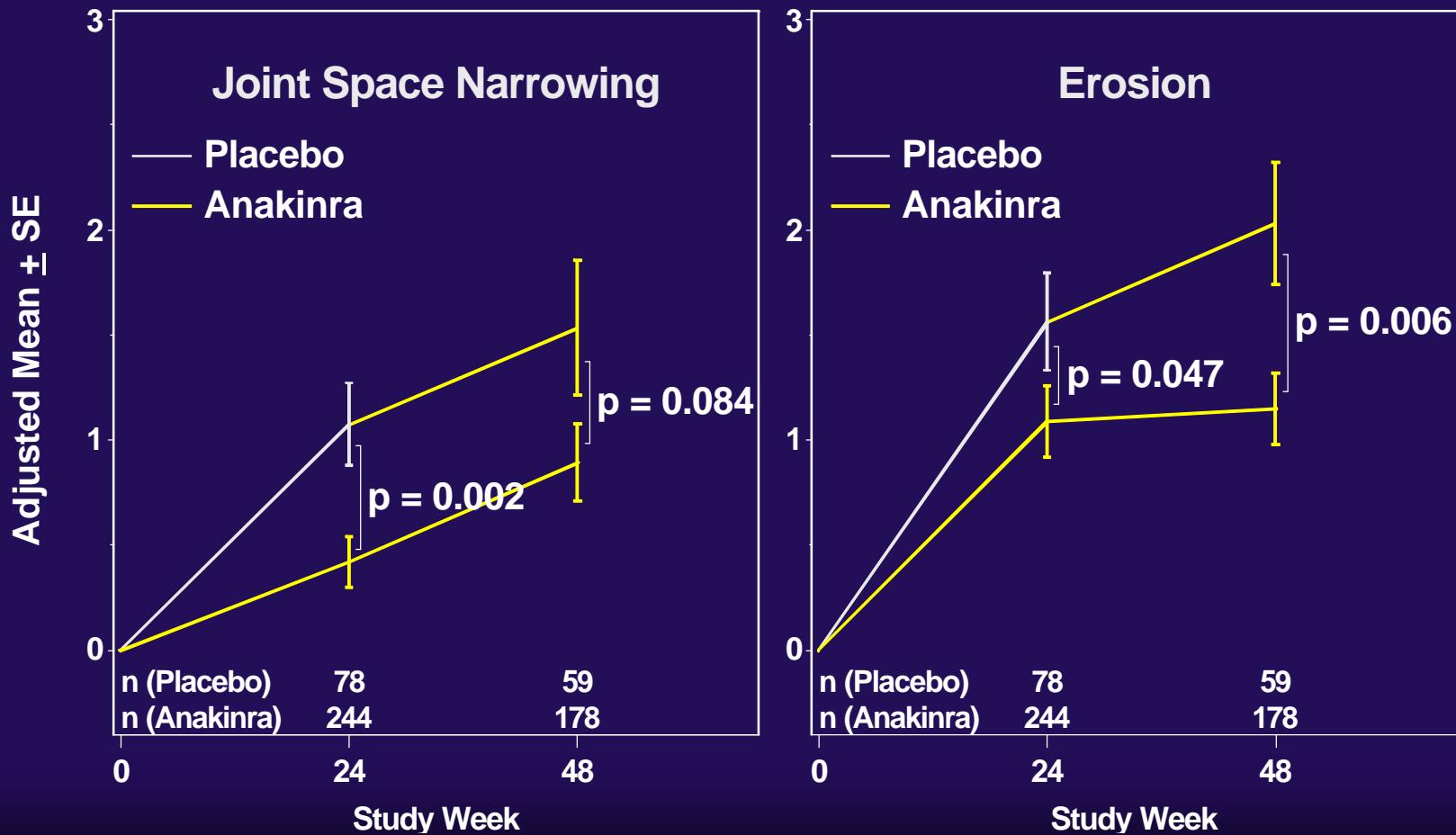
Change From Baseline
M-ITT Repeated Measure Mixed Model



Studies 0560 and 0564

Modified Sharp Score: Sub-scales

Change From Baseline
M-ITT Repeated Measure Mixed Model



Summary of Efficacy Results

- Effective in reducing the signs and symptoms of RA
 - 3 independent trials
 - Monotherapy and MTX combination
 - Results are robust and consistent
- Effects on radiographic disease progression are evident
 - Larsen Score
 - Modified Sharp Score

Agenda

- Overview
 - Roger M. Perlmutter, MD, PhD
- Clinical Experience
 - Moraye Bear, MS, MA
 - Pirow Bekker, MD, PhD
- Therapeutic Role of Anakinra
 - Stanley Cohen, MD

Anakinra Rheumatoid Arthritis Clinical Trials

Randomized, Placebo-controlled,
Blinded, Chronic Dosing

A = Anakinra
PI = Placebo

| |
|--|
| Confirmatory Efficacy 990145 A = 250; PI = 251 |
| Safety 990757 A = 1116; PI = 283 |
| Monotherapy 0560 A = 351; PI = 121 |
| MTX Combination 960180 A = 345; PI = 74 |
| Low Dose Mono 960182 A = 111; PI = 30 |

Anakinra Rheumatoid Arthritis Clinical Trials

Randomized, Placebo-controlled,
Blinded, Chronic Dosing

A = Anakinra
PI = Placebo

| | |
|--|---|
| Confirmatory Efficacy 990145 A = 250; PI = 251 | Single-Dose PK 0501 A = 20; PI = 5 |
| Safety 990757 A = 1116; PI = 283 | Multi-Dose PK 0502 A = 15 |
| Monotherapy 0560 A = 351; PI = 121 | 4-Day Cont. Infusion 970189 A = 40; PI = 10 |
| MTX Combination 960180 A = 345; PI = 74 | Dose & Frequency 0505 A = 175 |
| Low Dose Mono 960182 A = 111; PI = 30 | Cont. Infusion 980220 A = 18; PI = 3 |

Pharmacokinetic and
Supportive

Anakinra Rheumatoid Arthritis Clinical Trials

Randomized, Placebo-controlled,
Blinded, Chronic Dosing

A = Anakinra
PI = Placebo

| |
|---|
| Mono Extensions 0564, E1, E1, E3 <i>A = 309</i> |
| Combo Extension 960181 <i>A = 309</i> |
| Low Dose Extension 970102 <i>A = 112</i> |

| |
|---|
| Confirmatory Efficacy 990145 <i>A = 250; PI = 251</i> |
| Safety 990757 <i>A = 1116; PI = 283</i> |
| Monotherapy 0560 <i>A = 351; PI = 121</i> |

| |
|--|
| Single-Dose PK 0501 <i>A = 20; PI = 5</i> |
| Multi-Dose PK 0502 <i>A = 15</i> |
| 4-Day Cont. Infusion 970189 <i>A = 40; PI = 10</i> |

| |
|---|
| PK Extension 0502E <i>A = 11</i> |
| Dose&Freq. Ext. 0512 <i>A = 148</i> |

Pharmacokinetic and
Supportive

Anakinra Rheumatoid Arthritis RA Patients

| | Number of Patients | |
|---|---------------------------|-----------------|
| | Placebo | Anakinra |
| Randomized placebo-controlled studies and extensions | 759 | 2332 |
| Supportive studies | 3 | 199 |
| Pharmacokinetic studies | 15 | 75 |
| Total | 777 | 2606 |

Five Placebo-Controlled RA Studies Anakinra Experience By Dose

| | | Anakinra (mg) | | | |
|--|----------------------|--------------------|-------------------|--------------------|-------------------|
| | Placebo (N = 759) | < 100 (N = 610) | 100 (N = 1367) | > 100 (N = 196) | All (N = 2173) |
| Total exposure (patient-years)* | 296.2 | 214.7 | 559.3 | 70.9 | 845.0 |
| Median patient exposure (wks) | 24.0 | 23.9 | 24.4 | 24.0 | 24.1 |

*Includes studies 0560, 960180, 960182, 990145, 990757
Anakinra exposure in All RA Studies: 1873 patient-years

Points of Discussion

- Overall Adverse Event Profile
- Injection Site Reactions (ISRs)
- FDA questions
 - Infections
 - WBC profile
 - Anakinra/Etanercept Combination
 - Pediatric Study

Safety Data

Overall Adverse Event Profile

Five Placebo-Controlled Studies Safety Overview

| n (%) | Anakinra (mg) | | | | |
|---------------------------------|----------------------|--------------------|-------------------|--------------------|-------------------|
| | Placebo (N = 759) | < 100 (N = 610) | 100 (N = 1367) | > 100 (N = 196) | All (N = 2173) |
| Any AE | 645 (85.0) | 538 (88.2) | 1254 (91.7) | 190 (96.9) | 1982 (91.2) |
| AE Excl. ISR | 623 (82.1) | 491 (80.5) | 1088 (79.6) | 169 (86.2) | 1748 (80.4) |
| Serious AE | 49 (6.5) | 51 (8.4) | 97 (7.1) | 24 (12.2) | 172 (7.9) |
| Death^a | 1 (0.1) | 1 (0.2) | 4 (0.3) | 1 (0.5) | 6 (0.3) |
| Withdrawal due to AE | 88 (11.6) | 58 (9.5) | 186 (13.6) | 36 (18.4) | 280 (12.9) |

^aExcludes 1 death in Study 990145 due to blinded data

All RA Studies Deaths

19 subjects

| n/N (%) | Placebo | Anakinra |
|---------------------------------|-------------|--------------|
| Monotherapy Study | 0/121 (0.0) | 3/351 (0.9) |
| MTX Combination Study | 0/74 (0.0) | 0/345 (0.0) |
| Low Dose Monotherapy Study | 0/30 (0.0) | 0/111 (0.0) |
| Safety Study | 1/283 (0.4) | 4/1116 (0.4) |
| Confirmatory Efficacy Study | Blinded | 1/501 (0.2) |
| Uncontrolled Extension Studies* | | 10/913 (1.1) |

*Studies 0564, 0564E1, 0564E2, 960181, 0512

Five Placebo-Controlled Studies Serious Adverse Events (³ 0.2%)

| Preferred Term - n (%) | Anakinra (mg) | | | | | All (N = 2173) |
|-------------------------|----------------------|--------------------|-------------------|--------------------|-----------|-------------------|
| | Placebo (N = 759) | < 100 (N = 610) | 100 (N = 1367) | > 100 (N = 196) | | |
| Any | 49 (6.5) | 51 (8.4) | 97 (7.1) | 24 (12.2) | 172 (7.9) | |
| Worsening of RA | 12 (1.6) | 10 (1.6) | 10 (0.7) | 1 (0.5) | 21 (1.0) | |
| Pneumonia | 0 (0.0) | 2 (0.3) | 12 (0.9) | 0 (0.0) | 14 (0.6) | |
| Pain Abdominal | 2 (0.3) | 5 (0.8) | 4 (0.3) | 0 (0.0) | 9 (0.4) | |
| Arthralgia | 1 (0.1) | 3 (0.5) | 1 (0.1) | 2 (1.0) | 6 (0.3) | |
| Abdominal Hernia | 0 (0.0) | 0 (0.0) | 3 (0.2) | 2 (1.0) | 5 (0.2) | |
| Dyspnea | 0 (0.0) | 1 (0.2) | 4 (0.3) | 0 (0.0) | 5 (0.2) | |

All RA Studies

Malignancies

| n (rate per 100 pt yrs) | Placebo (N = 762) | Anakinra (N = 2531) |
|-----------------------------------|-----------------------------|-------------------------------|
| Any malignancy^a | 6 (2.02) | 21 (1.12) |
| Breast cancer^b | 0 (0.00) | 6 (0.42) |
| Basal cell carcinoma | 1 (0.34) | 4 (0.21) |
| Lung cancer | 2 (0.67) | 2 (0.11) |
| Prostate cancer | 0 (0.00) | 1 (0.22) |
| Thyroid cancer | 0 (0.00) | 2 (0.11) |
| Non-Hodgkin's lymphoma | 0 (0.00) | 1 (0.05) |
| Hodgkin's lymphoma | 1 (0.34) | 0 (0.00) |
| Other^c | 2 (0.67) | 5 (0.27) |

^a Excludes 2 recurring cancers and 1 prostate cancer in blinded study

^b Includes 2 non-infiltrating ductal carcinoma in situ

^c Anakinra: Pancreatic, cecal, oral, uterine, gastric cancer;
Placebo: Squamous cell skin carcinoma, bladder cancer

All RA Studies

Malignancies: Observed vs. Expected

| Exposure: 1873 patient years | All Anakinra | | |
|------------------------------|--------------|-------------|-----------------------|
| | Observed | 95% C.I. | Expected ^a |
| Total malignancies | 16 | 9.70, 26.22 | 15.6 |
| Leukemias | 0 | 0.00, 4.76 | 0.84 |
| Non-Hodgkin's lymphoma | 1 | 0.00, 6.38 | 0.58 |
| Women | | | |
| All malignancies | 9 | 4.51, 17.43 | 10.24 |
| Breast cancer | 4 | 1.21, 10.76 | 3.53 |
| Men | | | |
| All malignancies | 7 | 3.15, 14.70 | 5.38 |
| Prostate cancer | 2 | 0.10, 7.84 | 1.82 |

^a Based on National Cancer Institute's Surveillance Epidemiology and End Results (SEER) statistics

Five Placebo-Controlled Studies Withdrawals Due to Adverse Events (³ 0.3%)

| Preferred Term - n (%) | Placebo (N = 759) | Anakinra (mg) | | | | All (N = 2173) |
|---------------------------------------|------------------------------|-------------------------------|---------------------------|-------------------------------|------------|---------------------------|
| | | < 100 (N = 610) | 100 (N = 1367) | > 100 (N = 196) | | |
| Any | 88 (11.6) | 58 (9.5) | 186 (13.6) | 36 (18.4) | 280 (12.9) | |
| ISR | 10 (1.3) | 8 (1.3) | 100 (7.3) | 14 (7.1) | 122 (5.6) | |
| Worsening of RA/Arthralgia | 47 (6.2) | 29 (4.8) | 24 (1.8) | 9 (4.6) | 62 (2.9) | |
| Headache | 4 (0.5) | 0 (0.0) | 8 (0.6) | 0 (0.0) | 8 (0.4) | |
| Pain Abdominal | 3 (0.4) | 1 (0.2) | 7 (0.5) | 0 (0.0) | 8 (0.4) | |

Safety Data Injection Site Reactions

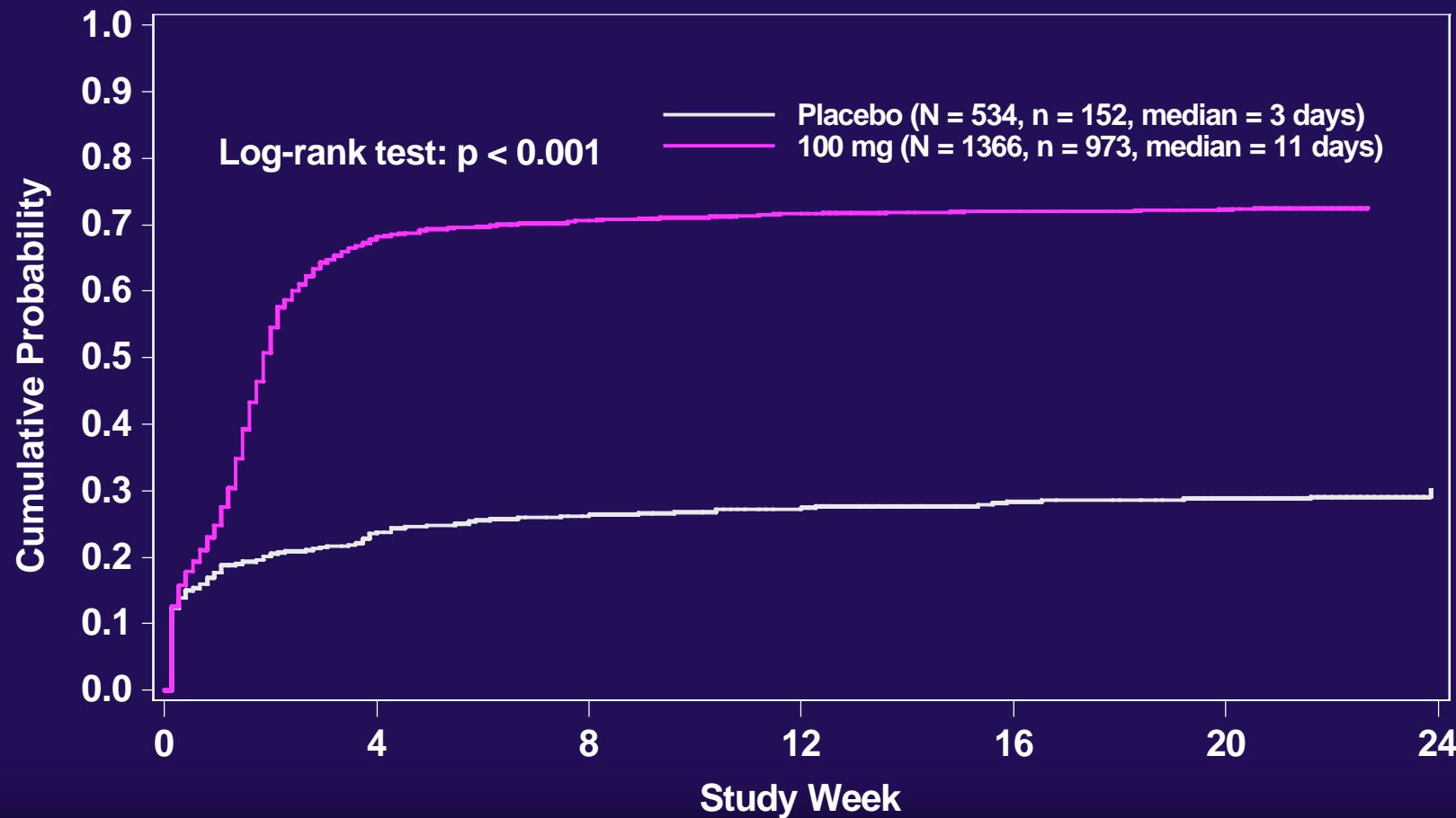
Five Placebo-Controlled Studies Injection Site Reactions (³ 10%)

| Preferred Term - n (%) | Anakinra (mg) | | | | | All (N = 2173) |
|--------------------------|----------------------|--------------------|-------------------|--------------------|-------------|-------------------|
| | Placebo (N = 759) | < 100 (N = 610) | 100 (N = 1367) | > 100 (N = 196) | | |
| Any | 204 (26.9) | 281 (46.1) | 973 (71.2) | 145 (74.0) | 1399 (64.4) | |
| Mild to moderate* | 198 (97.1) | 276 (98.2) | 923 (94.9) | 134 (92.4) | 1333 (95.3) | |
| Erythema | 35 (4.6) | 150 (24.6) | 505 (36.9) | 90 (45.9) | 745 (34.3) | |
| Pruritus | 14 (1.8) | 60 (9.8) | 412 (30.1) | 36 (18.4) | 508 (23.4) | |
| Rash | 10 (1.3) | 61 (10.0) | 315 (23.0) | 32 (16.3) | 408 (18.8) | |
| Pain | 93 (12.3) | 37 (6.1) | 250 (18.3) | 10 (5.1) | 297 (13.7) | |
| Ecchymosis | 94 (12.4) | 59 (9.7) | 200 (14.6) | 15 (7.7) | 274 (12.6) | |

* Incidence calculated for subjects with an ISR.

Safety and Confirmatory Efficacy Studies

Time to First Injection Site Reaction



All RA Studies

Anti-Anakinra Antibodies

- Only 10 of 1303 anakinra subjects (0.8%) positive in bioassay
 - potentially clinically neutralizing antibodies
- Positive at only 1 time point in all 10 subjects
- No apparent interference with efficacy or safety profile

Safety Data

Infections

Five Placebo-Controlled Studies Infectious Episodes

| n (%) | Placebo (N = 759) | Anakinra (mg) | | | | All (N = 2173) |
|-------------------|----------------------|--------------------|-------------------|--------------------|------------|-------------------|
| | | < 100 (N = 610) | 100 (N = 1367) | > 100 (N = 196) | | |
| Any | 275 (36.2) | 227 (37.2) | 544 (39.8) | 84 (42.9) | 855 (39.3) | |
| Serious* | 5 (0.7) | 7 (1.1) | 25 (1.8) | 4 (2.0) | 36 (1.7) | |
| Withdrawal | 6 (0.8) | 3 (0.5) | 16 (1.2) | 2 (1.0) | 21 (1.0) | |

* Includes hospitalization/extended hospitalization, life-threatening or fatal events, persistent/significant disability, medical intervention to prevent a life-threatening/fatal outcome.

Five Placebo-Controlled Studies Serious Infectious Episodes

| n (%) | Placebo (N = 759) | Anakinra (mg) | | | |
|--------------------------------|----------------------|--------------------|-------------------|--------------------|-------------------|
| | | < 100 (N = 610) | 100 (N = 1367) | > 100 (N = 196) | All (N = 2173) |
| Any* | 5 (0.7) | 7 (1.1) | 25 (1.8) | 4 (2.0) | 36 (1.7) |
| Pneumonia | 0 (0.0) | 2 (0.3) | 12 (0.9) | 0 (0.0) | 14 (0.6) |
| Cellulitis/Abscess | 1 (0.1) | 1 (0.2) | 7 (0.5) | 1 (0.5) | 9 (0.4) |
| Other Resp. Infection | 2 (0.3) | 2 (0.3) | 3 (0.2) | 1 (0.5) | 6 (0.3) |
| GI Infection | 1 (0.1) | 0 (0.0) | 3 (0.2) | 0 (0.0) | 3 (0.1) |
| Bursitis | 0 (0.0) | 1 (0.2) | 1 (0.1) | 1 (0.5) | 3 (0.1) |
| Urinary Tract Infection | 1 (0.1) | 1 (0.2) | 0 (0.0) | 1 (0.5) | 2 (0.1) |
| Osteomyelitis | 0 (0.0) | 0 (0.0) | 2 (0.1) | 0 (0.0) | 2 (0.1) |
| Pelvic Inflammation | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.7) | 1 (0.1) |
| Herpes Zoster | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.5) | 1 (0.0) |

* No cases of M. tuberculosis, Pneumocystis carinii, Listeria monocytogenes, Histoplasmosis

Five Placebo-Controlled Studies Serious Pneumonia

| Age, Sex | Description | Medical History | Concomitant Meds | Outcome |
|----------|---|--------------------------------------|--------------------|-----------|
| 42 F | Pneumonia | None | Prednisone, MTX | Withdrawn |
| 56 F | R. mid lobe pneum. | COPD, asthma | MTX | Continued |
| 77 M | Interstitial pneum. | None | Prednisone, MTX | Continued |
| 64 M | Pneumonia | COPD, asthma | Methyl-pred., MTX | Continued |
| 62 M | R. low lobe pneum. | CAD, CHF, CABG | None | Continued |
| 66 M | L. low lobe pneum. | Atopy, pneumonia, asthma, CHF | Prednisone, MTX | Continued |
| 59 F | R. lung pneum., pl. effusion, empyema | Dyspnea, atopy, asthma, pneumonia | Methylprednisolone | Continued |
| 46 M | L. lung pneumonia | Pneumonia, COPD, bronchiectasis | Prednisone, MTX | Withdrawn |
| 51 F | Pneumonia | None | Prednisone, azath. | Continued |
| 62 F | Bronchopneumonia | Asthma | Prednisone, MTX | Continued |
| 72 M | Strep. pneumonia (L. lung infiltrates) | Dyspnea, COPD, pulm. fibrosis | Prednisone, azath. | Withdrawn |
| 64 F | L. low lobe pneum. | None | None | Withdrawn |
| 64 F | Pneumonia, CHF | CAD, COPD | Pred., MTX, HCQ | Continued |
| 66 F | Legionella pneum. (L. lower lobe) | None | Prednisone, MTX | Withdrawn |

Five Placebo-Controlled Studies Characteristics of Serious Pneumonia

| | With Pneumonia (N = 14) | All Anakinra (5 PC studies) (N = 2173) |
|------------------------------------|-------------------------------|--|
| Age, mean (SD) | 60.8 (9.5) | 54.2 (12.4) |
| Time to onset (days): mean, median | 88.2, 79.5 | |
| Duration (days): mean, median | 17.4, 11.5 | |
| Deaths | 0 (0.0%) | |
| Withdrawn from study | 5 (35.7%) | |
| Relevant medical history, n (%) | 8 (57.1%) | |
| Asthma, n (%) | 5 (35.7%) | 177 (8.1%) |
| COPD, n (%) | 5 (35.7%) | 255 (11.7%) |
| Pneumonia, n (%) | 3 (21.4%) | 162 (8.4%) |
| Relevant concomitant meds, n (%) | 12 (85.7%) | |
| Corticosteroids, n (%) | 11 (78.6%) | 1235 (56.8%) |
| Methotrexate, n (%) | 9 (64.3%) | 1219 (56.1%) |
| Other DMARDs, n (%) | 3 (21.4%) | 632 (29.1%) |

Five Placebo-Controlled Studies Serious Infections: Risk Factors Evaluated

- Demographics:
 - age
 - gender
 - weight
- Duration of RA
- Concomitant medications:
 - corticosteroids
 - corticosteroid dose
 - methotrexate
 - other DMARDs
- Medical history:
 - asthma
 - COPD
 - CHF
 - CAD
 - diabetes mellitus
 - pneumonia
- Neutrophil decrease

Five Placebo-Controlled Studies Serious Infection by History of Asthma

| n (%) | Placebo | | Anakinra | |
|--------------------------|-----------------|-----------------|------------------|------------------|
| | No (N = 709) | Yes (N = 50) | No (N = 1996) | Yes (N = 177) |
| Serious Infection | 5 (0.7) | 0 (0.0) | 28 (1.4) | 8 (4.5) |
| Serious Pneumonia | 0 (0.0) | 0 (0.0) | 9 (0.5) | 5 (2.8) |

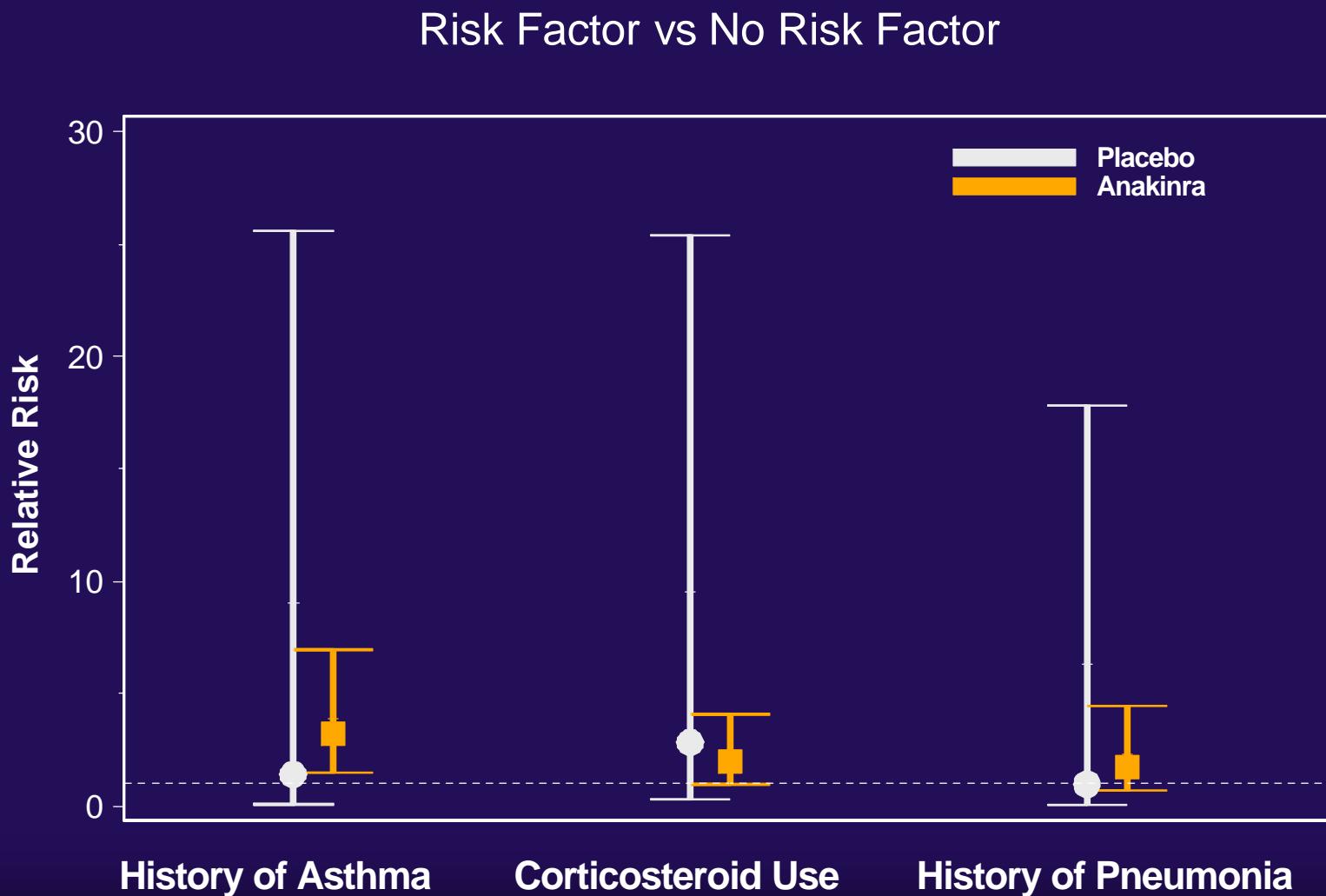
Five Placebo-Controlled Studies Serious Infection by History of Pneumonia

| n (%) | Placebo | | Anakinra | |
|--------------------------|-----------------|-----------------|------------------|------------------|
| | No (N = 689) | Yes (N = 70) | No (N = 1990) | Yes (N = 183) |
| Serious Infection | 5 (0.7) | 0 (0.0) | 31 (1.6) | 5 (2.7) |
| Serious Pneumonia | 0 (0.0) | 0 (0.0) | 11 (0.6) | 3 (1.6) |

Five Placebo-Controlled Studies Serious Infection by Corticosteroid Use

| n (%) | Placebo | | Anakinra | |
|--------------------------|--------------------|--------------------|---------------------|----------------------|
| | Not Use | Use | Not Use | Use |
| Serious Infection | N = 316 1 (0.3) | N = 443 4 (0.9) | N = 938 10 (1.1) | N = 1235 26 (2.1) |
| Serious Pneumonia | N = 316 0 (0.0) | N = 443 0 (0.0) | N = 938 3 (0.3) | N = 1235 11 (0.9) |

Five Placebo-Controlled Studies Serious Infections: Risk Factor Assessment



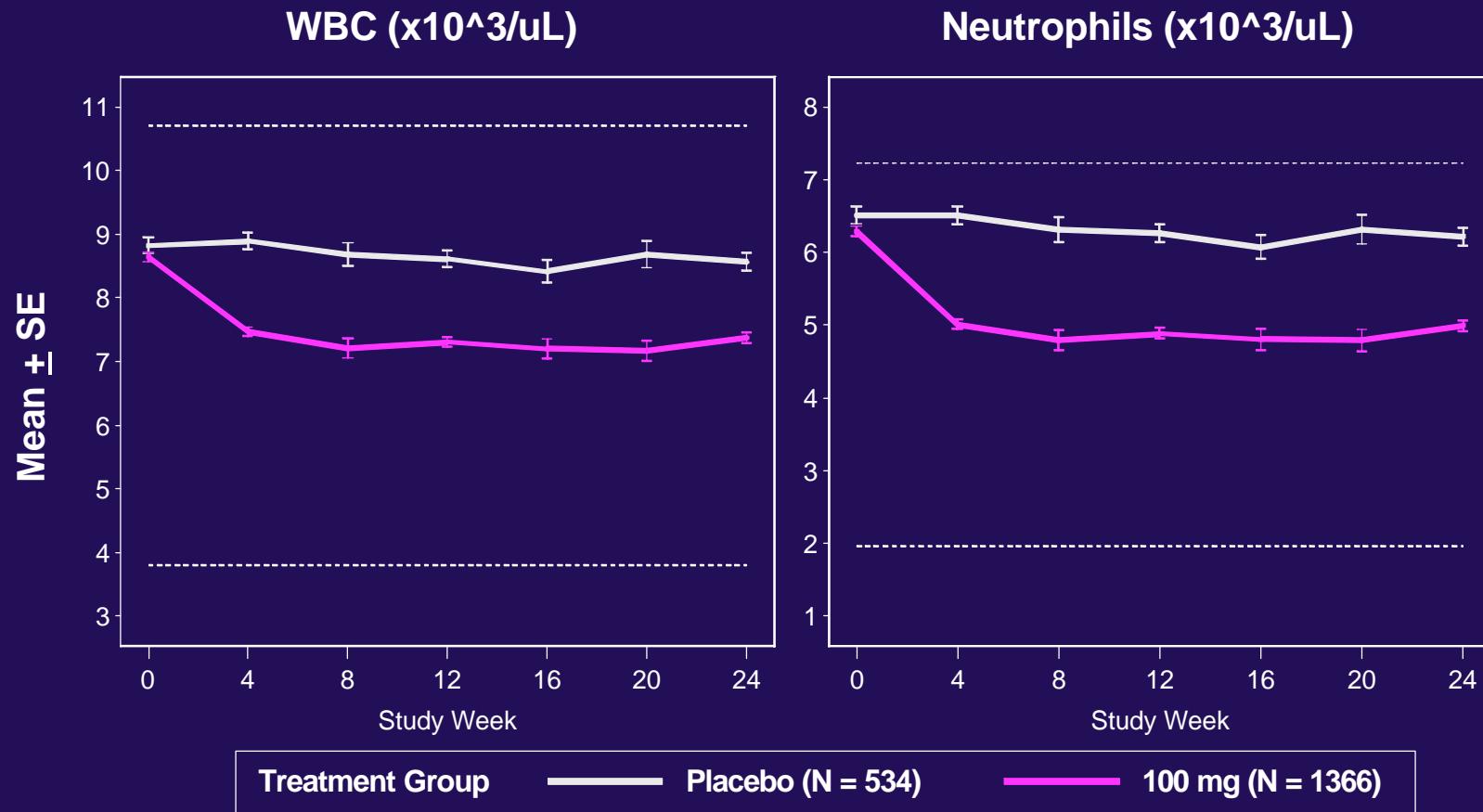
Five Placebo-Controlled Studies Most Common Infectious Events (³ 5.0%)

| Pref . Term - n (%) | Anakinra (mg) | | | | |
|---------------------|----------------------|--------------------|-------------------|-------------------|-------------------|
| | Placebo (N = 759) | < 100 (N = 610) | 100 (N = 1367) | >100 (N = 196) | All (N = 2173) |
| Upper Resp. Infect. | 95 (12.5) | 63 (10.3) | 174 (12.7) | 23 (11.7) | 260 (12.0) |
| Sinusitis | 36 (4.7) | 25 (4.1) | 86 (6.3) | 8 (4.1) | 119 (5.5) |
| Flu-Like Symptoms | 35 (4.6%) | 29 (4.8) | 74 (5.4) | 14 (7.1) | 117 (5.4) |

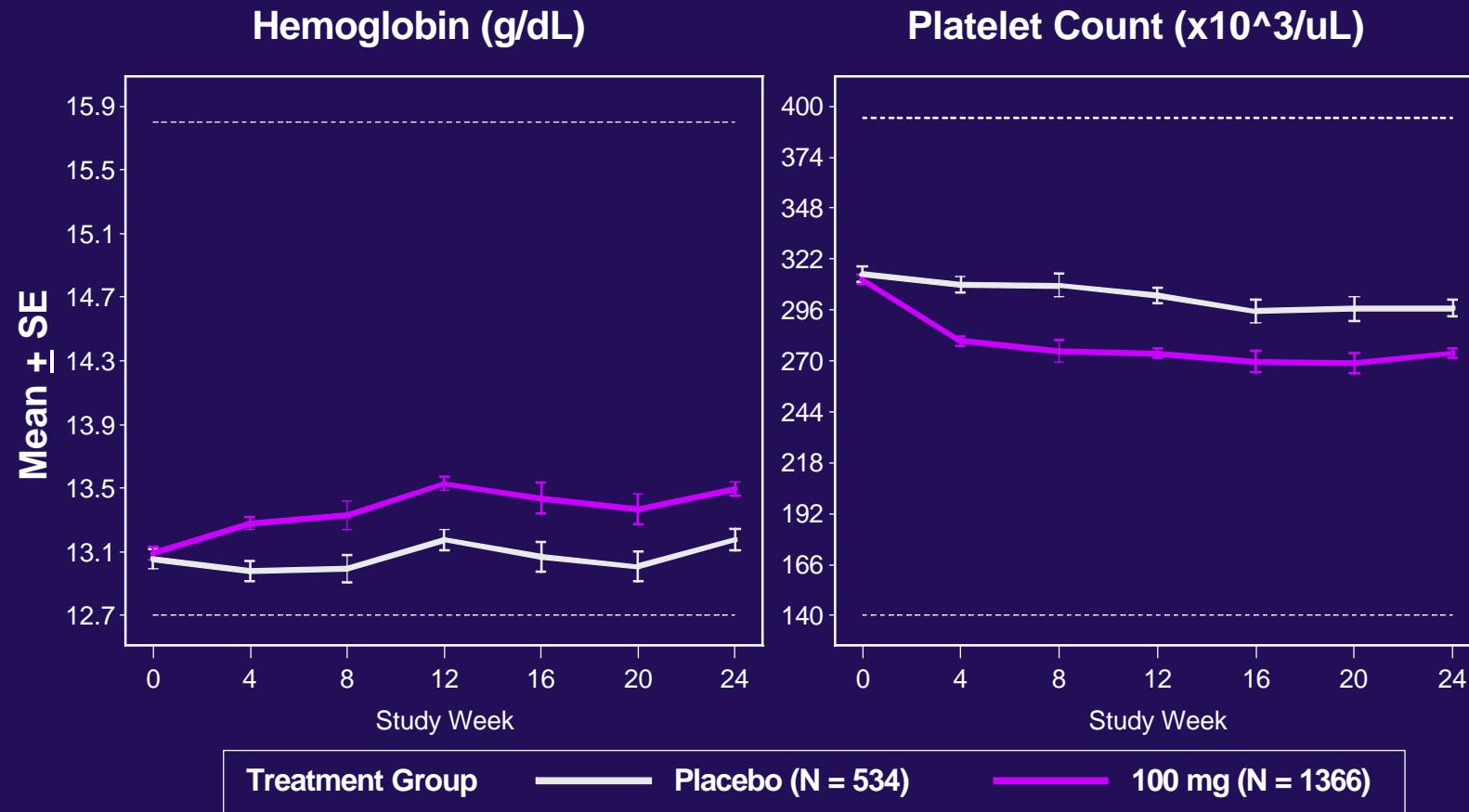
Safety Data WBC Profile

Safety and Confirmatory Efficacy Studies

WBC and Neutrophil Counts



Safety and Confirmatory Efficacy Studies Hemoglobin and Platelet Counts



Five Placebo-Controlled Studies

WBCs and Neutrophils (WHO Tox Grades)

| WHO Tox Grade - n (%) | Placebo | Anakinra (mg) | | | | All |
|---------------------------------|---------|---------------|----------|-------------|---------|----------|
| | | < 100 | 100 | > 100 | | |
| WBC decrease | | N = 739 | N = 609 | N = 1308 | N = 191 | N = 2108 |
| 2 ($2 - 3 \times 10^9/L$) | | 2 (0.3) | 12 (2.0) | 17 (1.3) | 5 (2.6) | 34 (1.6) |
| 3 ($1 - 2 \times 10^9/L$) | | 0 (0.0) | 1 (0.2) | 0 (0.0) | 0 (0.0) | 1 (0.1) |
| 4 ($< 1 \times 10^9/L$) | | | | None | | |
| Neutrophil decrease | | N = 736 | N = 609 | N = 1303 | N = 191 | N = 2103 |
| 2 ($1.0 - 1.5 \times 10^9/L$) | | 2 (0.3) | 5 (0.8) | 26 (2.0) | 3 (1.6) | 34 (1.6) |
| 3 ($0.5 - 1.0 \times 10^9/L$) | | 0 (0.0) | 4 (0.7) | 1 (0.1) | 1 (0.5) | 6 (0.3) |
| 4 ($< 0.5 \times 10^9/L$) | | | | None | | |

N = Number of evaluable subjects with baseline and post baseline WHOTOX grades

All RA Studies

Subjects with Neutrophil Count < 1 x 10⁹/L (1)

| Study | Age Sex | Dose | Day | Bl. ANC | Lowest ANC | Duration (days) | Last ANC | Comments |
|--------|---------|------------|-----|---------|------------|-----------------|------------------|--------------------------------------|
| 960180 | 63 M | 0.4 mg/kg | 24 | 1.73* | 0.96 | 4 | 1.48 | Withdrawn |
| | 63 F | 0.04 mg/kg | 148 | 1.74* | 0.90 | 23 | 2.71 | Withdrawn |
| | 62 F | 0.4 mg/kg | 88 | 2.94 | 0.56 | Unk. | 0.56 (End Study) | Tooth and eye infection, oral ulcers |
| 0560 | 52 F | 75 mg | 57 | 2.35 | 0.95 | 4 | 2.27 | Not withdrawn |

*Baseline below 2 x 10⁹/L; ANC = absolute neutrophil count;
 Bl. = baseline; Unk. = unknown

All RA Studies

Subjects with Neutrophil Count < 1 x 10⁹/L (2)

| Study | Age Sex | Dose | Day | Bl. ANC | Lowest ANC | Duration (days) | Last ANC | Comments |
|--------|------------|-----------------------|-----|------------|---------------|--------------------|-------------|--------------------------------|
| 0560 | 62 M | 150 mg | 8 | 1.90* | 0.91 | 9 | 1.06 | Chest infection, not withdrawn |
| 990757 | 58 F | 100 mg | 85 | 2.53 | 0.79 | 6 | 1.53 | Withdrawn |
| 0501 | Unk. F | 6.0 mg/kg | 6h | 1.76* | 0.78 | 6.75 | 1.41 | |
| 0502 | 58 F | 4.0 & 1.0 mg/kg | 11 | 1.03* | 0.27 | Unk. | 0.41 | Probable Felty, withdrawn |

*Baseline below 2 x 10⁹/L; ANC = absolute neutrophil count;
 Bl. = baseline; unk. = unknown

All RA Studies

Withdrawals due to Leukopenia/Granulocytopenia

Protocol-mandated withdrawal in earlier studies:

| | WBC Count | Neutrophil Count |
|-----------------------------------|----------------------------|----------------------------|
| Monotherapy Study, Extension: | < 3.5 x 10 ⁹ /L | < 2.0 x 10 ⁹ /L |
| MTX Combination Study, Extension: | < 3.0 x 10 ⁹ /L | < 1.5 x 10 ⁹ /L |

- 17 of 2606 subjects (0.7%)
- One severe neutropenia (< 0.5 x 10⁹/L); Felty syndrome
- 7 of 17 (41.2%) received > 100 mg anakinra
- 2 of 17 (11.8%) neutrophil count never < 2.0 x 10⁹/L
- 4 of 17 (23.5%) neutrophil count < 1.0 x 10⁹/L
- No serious infections
- 2 UTI cases; 1 head cold

Five Placebo-Controlled Studies Infection by Neutrophil Count < $1.5 \times 10^9/L$

| n (%) | Placebo | | Anakinra | |
|--------------------------|-----------------|----------------|------------------|-----------------|
| | No (N = 757) | Yes (N = 2) | No (N = 2126) | Yes (N = 47) |
| Serious Infection | 5 (0.7) | 0 (0.0) | 36 (1.7) | 0 (0.0) |
| Serious Pneumonia | 0 (0.0) | 0 (0.0) | 14 (0.7) | 0 (0.0) |

All RA Studies

WBC Profile

- In summary, severe neutropenia ($< 0.5 \times 10^9/L$)
 - occurred rarely (0.04%); 1 subject with probable Felty
- Neutrophil decrease below $1.0 \times 10^9/L$
 - occurred uncommonly (0.31%)
 - mostly (62.5%) in subjects neutropenic at baseline ($< 2.0 \times 10^9/L$)
 - did not lead to serious or severe infections
 - was transient (median 7 days)
 - was reversible in all subjects with available follow-up data

Safety Data

Anakinra/Etanercept Combination

Study 20000125

Anakinra/Etanercept Combination Study

| | |
|-------------------|---------------------------------------|
| Design: | Open-label, single arm |
| | Patients on etanercept (25 mg BIW SC) |
| Dosage: | 1 mg/kg/d SC anakinra |
| Patients: | 58 |
| Duration: | 24 weeks |
| Location: | US |
| Primary endpoint: | Serious Adverse Events |

Anakinra/Etanercept Combination Study

Baseline Characteristics

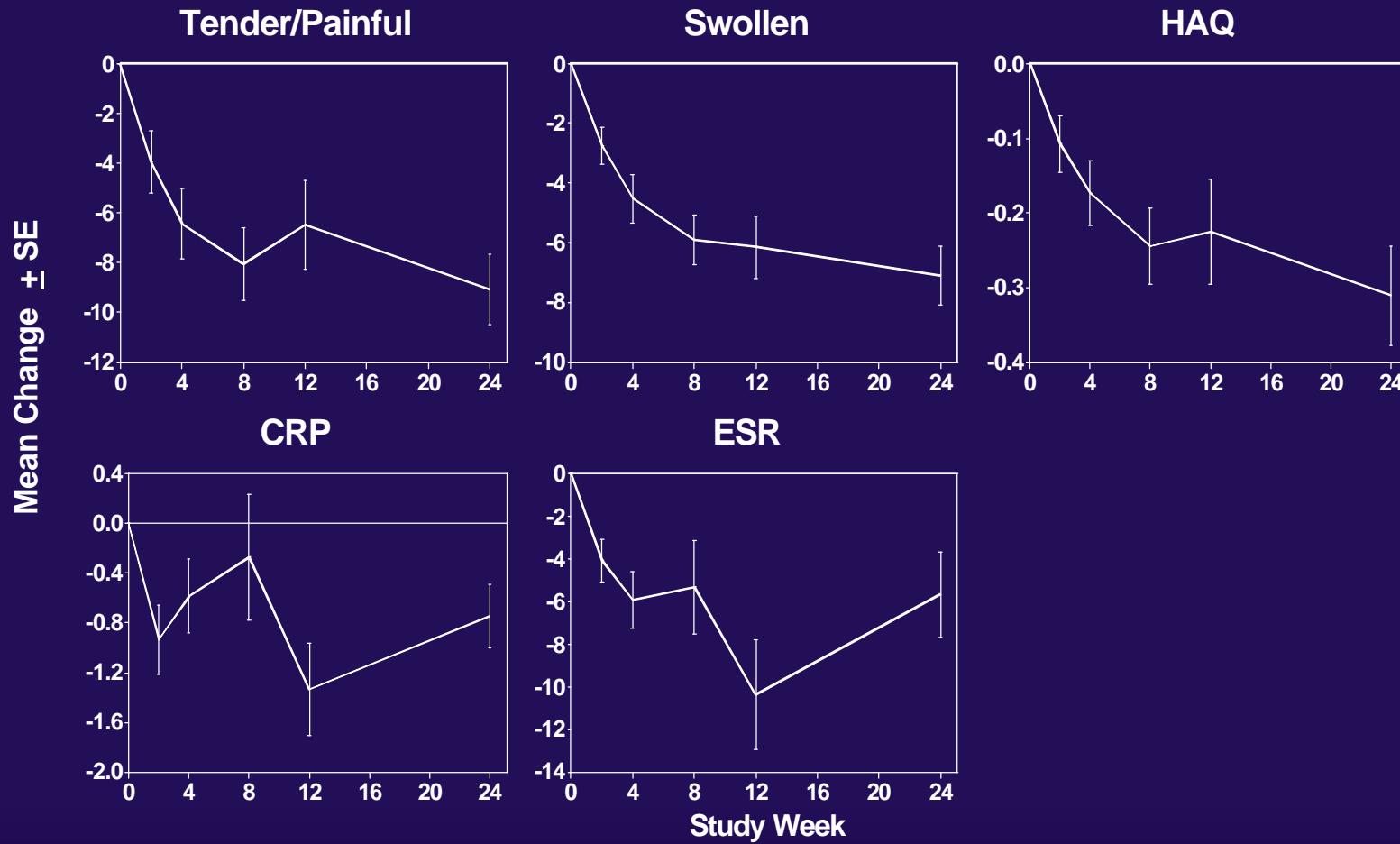
| | Anakinra (N = 58) |
|----------------------------|------------------------------|
| Mean (SD) | |
| Age | 48.9 (10.1) |
| Women, n (%) | 49 (84.5%) |
| Years on etanercept | 1.2 (0.7) range 0.2 – 3.2 |
| Years with RA | 11.9 (8.0) |
| Tender/painful joint count | 26.4 (14.0) |
| Swollen joint count | 17.4 (7.3) |
| CRP (mg/dL) | 2.2 (2.8) |

Anakinra/Etanercept Combination Study

Adverse Events

- No deaths
- 7 (12.1%) serious adverse events
 - Cellulitis 2
 - Pneumonia 2
 - Accidental electrocution 1
 - Opiate, barbiturate withdrawal 1
 - Gastric ulcer hemorrhage 1

Anakinra/Etanercept Combination Study ACR Components



Safety Data

Juvenile Rheumatoid Arthritis Study

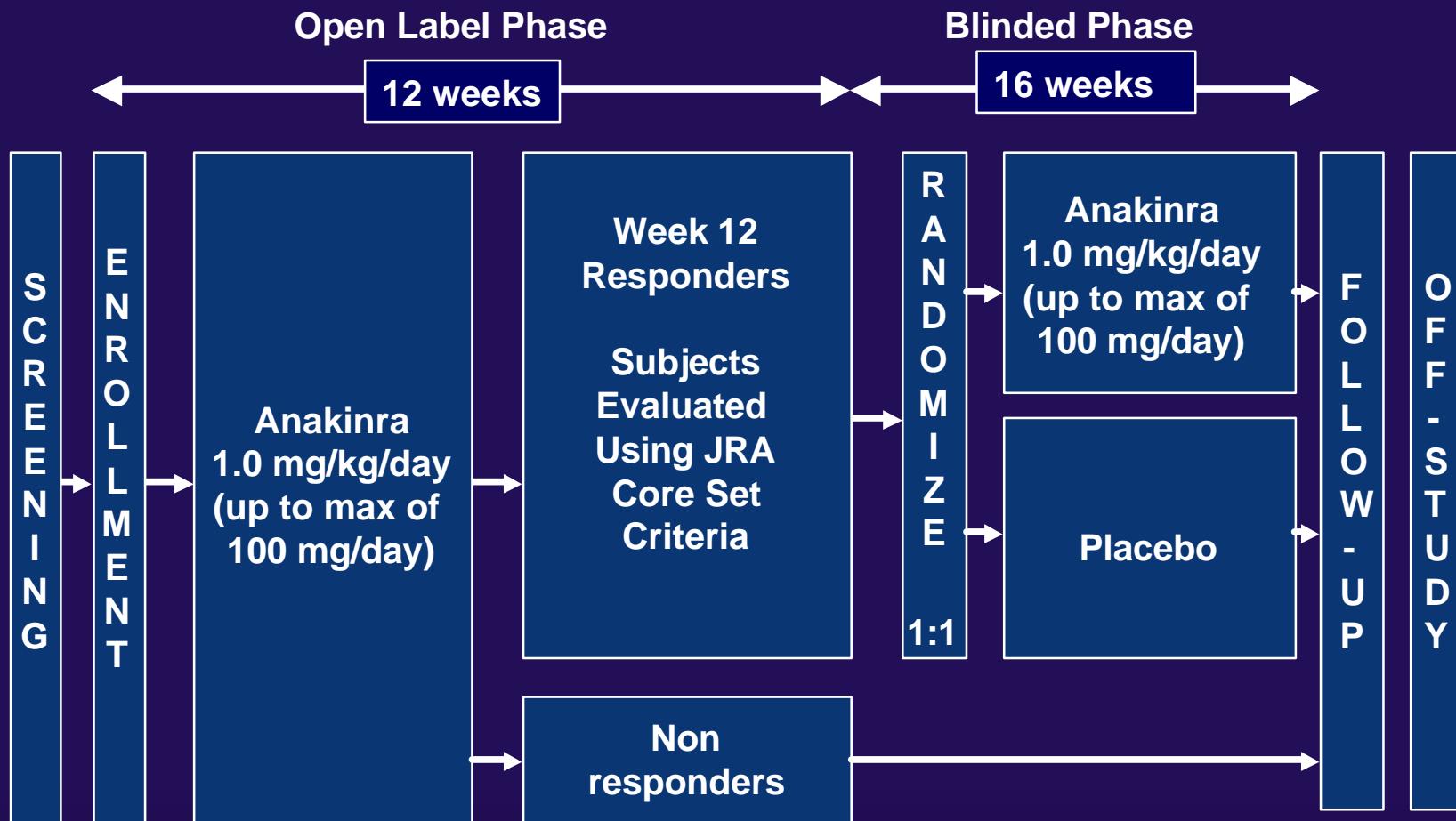
Study 990758

Juvenile Rheumatoid Arthritis Study

| | |
|-------------------|--|
| Design: | Randomized study Stage 1: 12 weeks open-label Stage 2: 16 weeks blinded, placebo-controlled |
| Dosage: | 1 mg/kg/d SC anakinra (up to 100 mg) |
| Patients: | Stage 1: 204 targeted Stage 2: 68 |
| Duration: | 30 weeks (including 2 weeks follow-up) |
| Location: | North and South America, Europe, and Australia |
| Primary endpoint: | Disease flare during blinded period |

Juvenile Rheumatoid Arthritis Study

Study Schema



Anakinra

Safety Summary and Conclusions

- Large anakinra safety database:
 - 2606 RA patients received at least 1 anakinra dose
 - 1873 patient years total anakinra exposure
- Serious infections:
 - Low incidence; Anakinra (1.7%), Placebo (0.7%)
 - Mostly pneumonia
 - Risk possibly higher in patients with asthma
- Neutrophil decrease below $1.0 \times 10^9/\text{L}$:
 - Rare (0.31%) in anakinra patients
 - Reversible and not of clinical consequence
- In conclusion, anakinra has a favorable safety profile

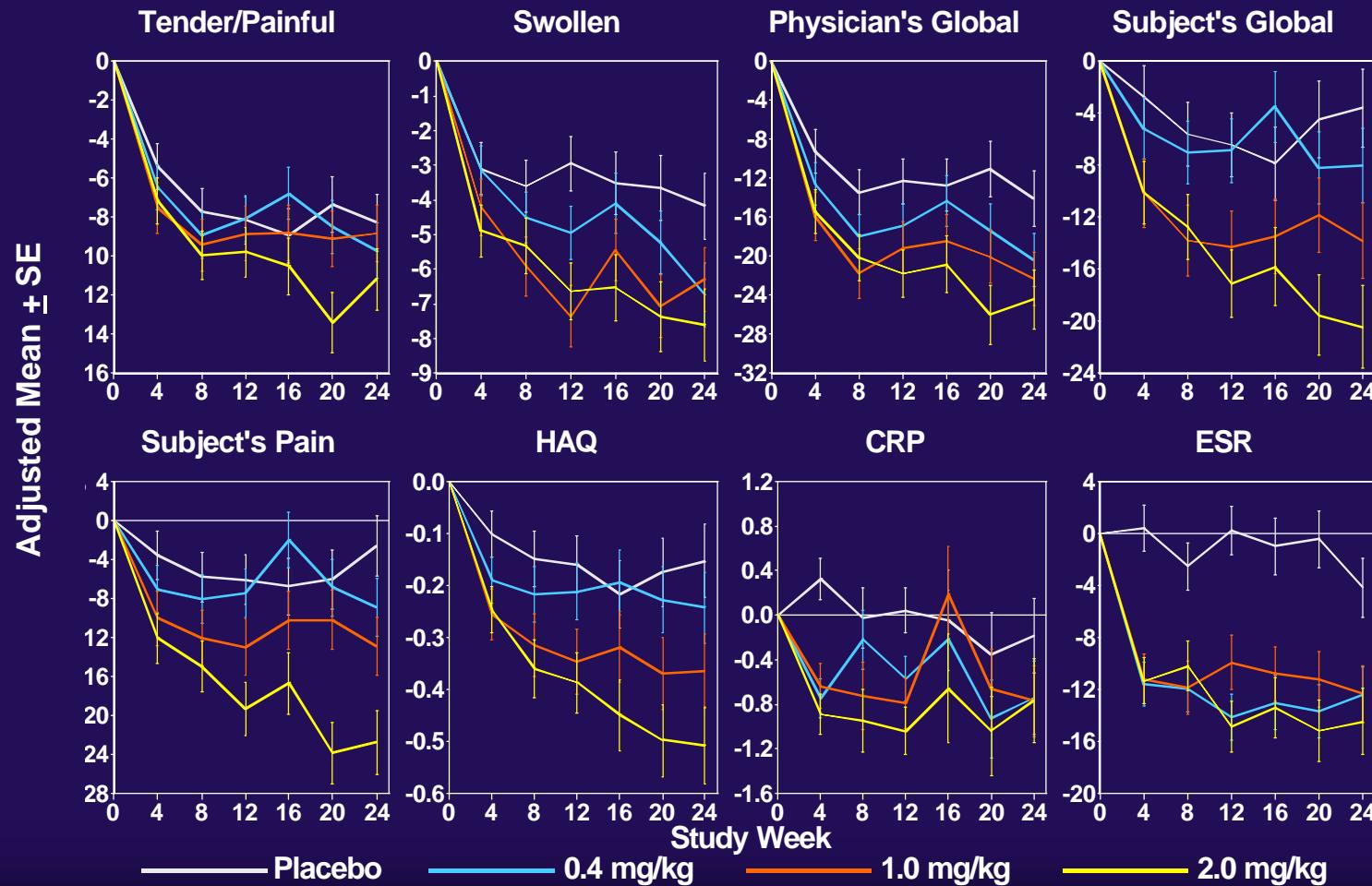
Agenda

- Overview
 - Roger M. Perlmutter, MD, PhD
- Clinical Experience
 - Moraye Bear, MS, MA
 - Pirow Bekker, MD, PhD
- Therapeutic Role of Anakinra
 - Stanley Cohen, MD

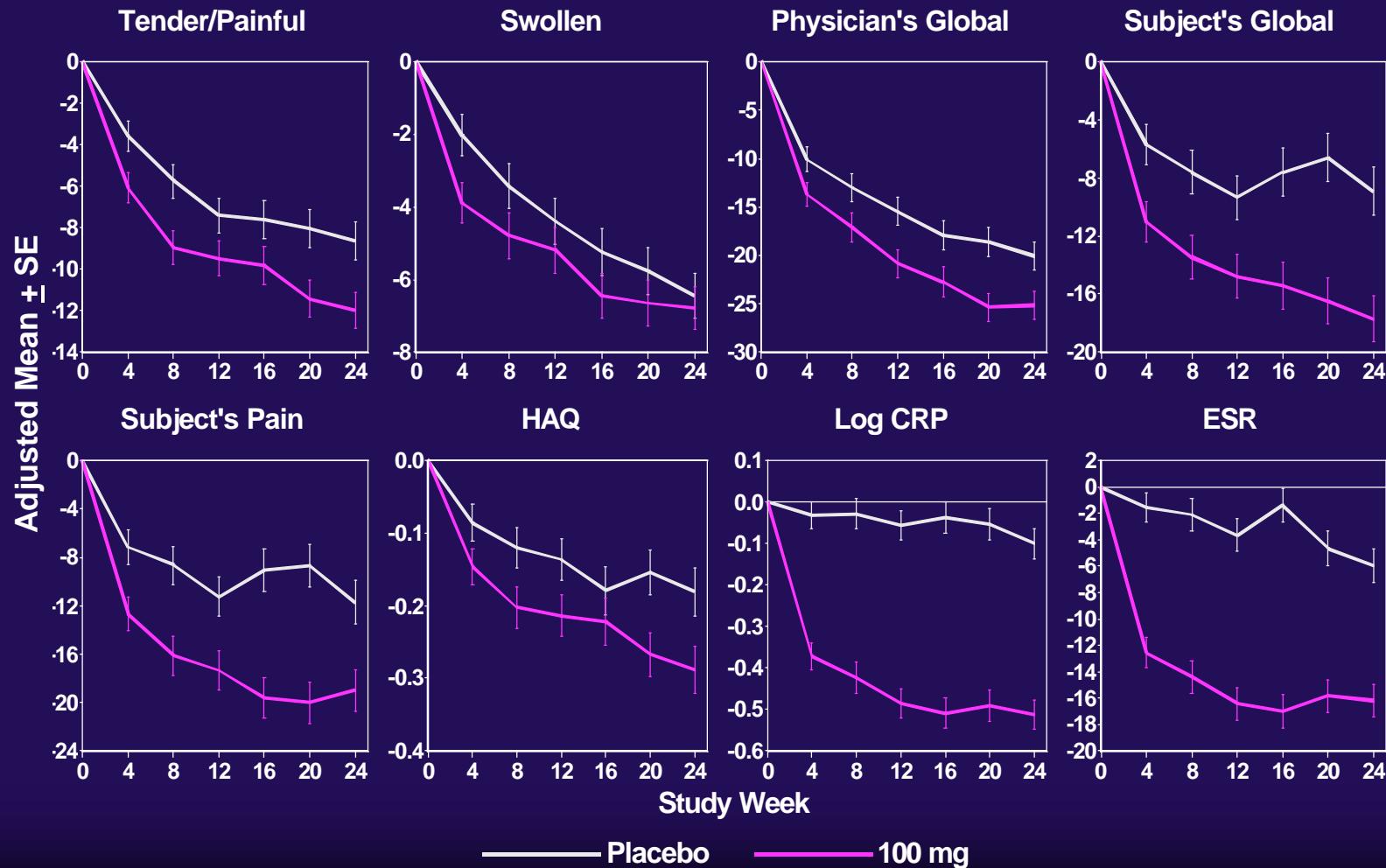
Need for Future Therapies

- ACR₂₀ responses for biologics and newer therapies in range of 40 to 70%
 - 30 to 60% of patients still have active disease
- Chart review
 - Within 9 months, 20/131 patients started on Infliximab discontinued therapy; similar drop off rate for Etanercept

Study 960180 (MTX Combination) Individual ACR Components by Study Week

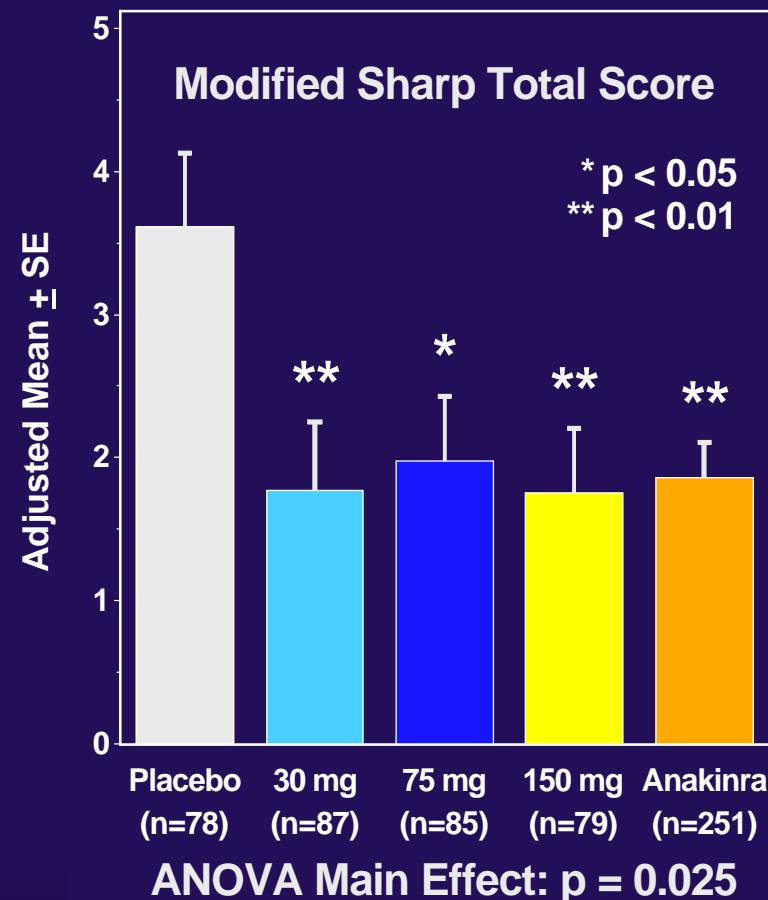


Study 990145 (Confirmatory Efficacy Study) Individual ACR Components by Study Week



Study 0560 (Monotherapy) Modified Sharp Total Scores

24-week Change From Baseline



Anakinra Risk-Benefit Assessment

Risks

- Injection site reactions
- Serious infections
- Rare decreases in WBCs
- Daily Injectable
 - Favorable patient compliance in studies

Practical Guidance for Looking After Anakinra Patients

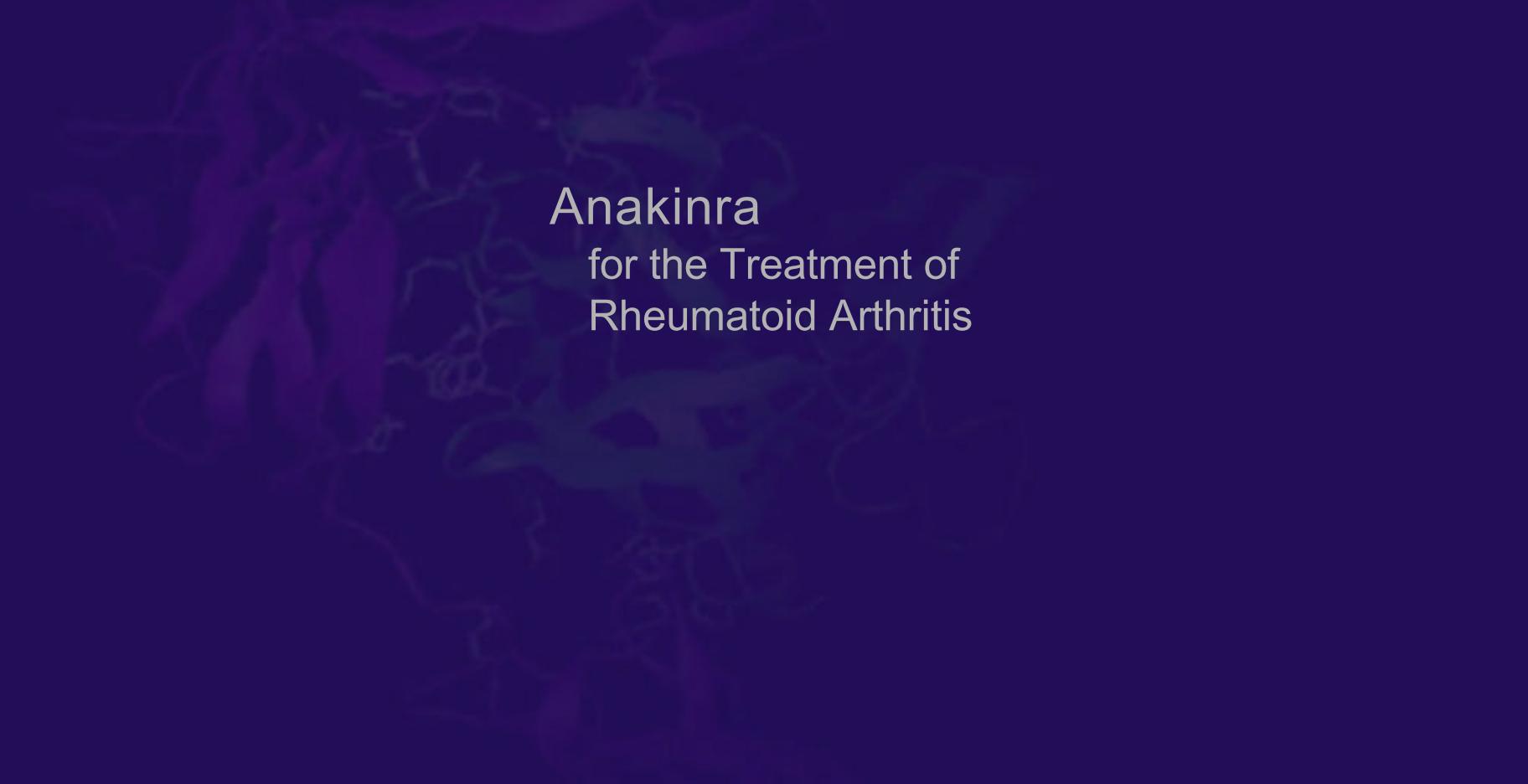
- Proper patient selection
 - Patients with moderate to severe RA
 - Avoid patients with acute or chronic infection
- Proper patient education
 - Injection site reactions
 - Infection precautions
- Patients with a low baseline neutrophil count should be monitored

Which Patients Should Get Anakinra?

- DMARD failures
 - Use as a monotherapy
- Patients who lack full response to DMARDs
 - Use in combination therapy
- Patients who lack full response to biologic agents
 - With more data, future combination of biologic agents

Summary: Anakinra Therapy

- Unique mechanism of action
 - First IL-1 inhibitor for rheumatoid arthritis
- Naturally-occurring anti-inflammatory
- Favorable Risk/Benefit profile
 - ACR benefit—early and sustained
 - Important effects on patient-reported outcomes
 - Effects on radiographic disease progression are evident
 - Rapid clearance upon discontinuation of therapy



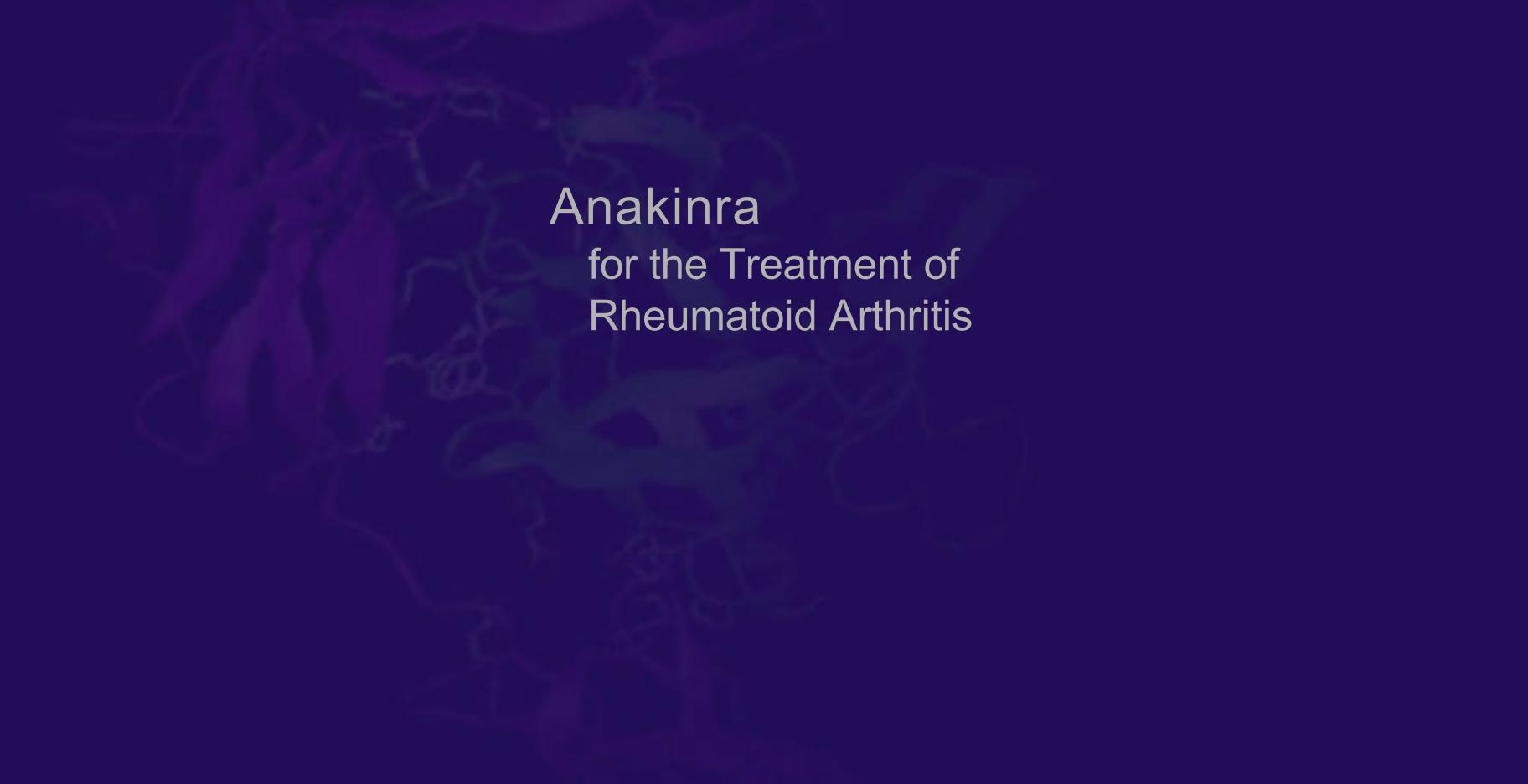
Anakinra for the Treatment of Rheumatoid Arthritis

August 16, 2001

Proposed Indication for Anakinra

Anakinra is indicated for the reduction in signs and symptoms of active rheumatoid arthritis, in patients 18-years of age or older who have failed 1 or more disease-modifying antirheumatic drugs (DMARDs).

Anakinra can be used alone or in combination with other DMARDs.



Anakinra for the Treatment of Rheumatoid Arthritis

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